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EXPERIENCES ASSOCIATED WITH A TRANSFUSION UNIT IN A 700 BED HOSPITAL: AN ANNUAL SURVEY OF OVER 3,500 ADMINISTRATIONS OF BLOOD AND PLASMA (DRIED) *

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THE purpose of this analysis is to discuss some of the clinical experiences and the practical problems associated with the Blood Transfusion-Plasma Unit † of Jefferson Hospital for the year ending July 1, 1942.

TECHNIC

a. Preparation of Blood and Equipment Used. During the year no bottle of blood was used for a transfusion after four days of storage. Many of the qualities of blood change after that period of storage.[1, 2] Since there were relatively few colored donors, colored blood was given to colored patients or used for plasma.[3] Blood was typed and crossmatched by the Landsteiner technic. The apparatus for collecting and dispensing blood (including cellulose tubing) was purchased from Hospital Liquids Incorporated; both the 750 c.c. vacuum bottles and the 650 c.c. centrifuge vacuum bottles were used. Because rubber tubing is becoming scarce and because the danger of pyrogens is probably minimized in cellulose tubing, which is discarded after the initial use, cellulose tubing was used for the administration of blood and has proved to be a very satisfactory substitute. All of the blood transfused was citrated and was administered cold as it came from the ice box, the temperature of which was maintained at 35° F.

A card attached to each bottle of blood taken from the bank had the name of the donor, the date the blood was withdrawn, the type of blood contained, the results of the serologic tests (both Kahn and Wassermann), the name of

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the recipient and the name of the technician who performed the crossmatching. After each transfusion the attending nurse must sign the card attached to the bottle indicating that the patient did or did not have a reaction following the transfusion. Of 2,869 transfusions during the year, in only three instances was blood administered other than the type identical to that of the patient's (3 bottles of citrated blood of type "O" were given to three patients with type "A" blood) and of the three, one patient suffered a hemolytic reaction (see case reports). We feel that homologous blood should be administered but there is good evidence that blood from universal donors is usually safe. Rosenthal and Vogel[4a] have shown that in over 800 transfusions of universal donor blood no more reactions occurred than when homologous bank blood, or when the old indirect transfusions of homologous blood were used.

Aubert et al.[5] demonstrated that in 40 per cent of donors of group "O," anti-A titers of over 1:512 were found and noted that transfusions of "O" blood of such high anti-A titer, or higher, rarely produced an elevation of the red blood cell levels of recipients of group "A." Neither did they produce severe or fatal hemolytic reactions. They concluded that when a transfusion is designed to raise a recipient's red cell count homologous group blood should be given, but in emergencies when restoration of blood volume is required universal donor blood is justified.

The technic followed for cleaning needles and rubber tubing was described by Lewisohn and Rosenthal.[6, 1] The scrupulous cleanliness of these articles was found to be of the utmost importance in preventing post-transfusional febrile reactions.

b. Plasma. The outdated blood, that after four days of storage, was either separated (DeLaval separator) or centrifuged, the plasma withdrawn (either by the open or closed systems), then pooled to reduce agglutinin titer, frozen in glass containers, dried by the Hill Adtevac machine [7] (a most practical machine since the hydroscopic agent, silica gel, can be used over and over again) and weighed out in 12.5 or 16 gram quantities and placed in glass vials with rubber stoppers, from which the air was evacuated or the air was replaced with CO_2 gas. Twelve and one half to 16 grams represent the average amounts of dried plasma obtained from 500 c.c. of blood. The small vial (120 c.c.) containing the plasma and another small vial (60 c.c.) containing pyrogen-free water can easily be carried in the coat pocket of a physician (figure 1). With the aid of a 50 c.c. syringe and needle any physician can have the equivalent of a pint of blood (excluding red blood cells) available at any moment. Such 4 or 5 fold concentrated plasma is popular because it can be administered within three to five minutes of time. The water used for the restoration of the dried plasma was obtained from an electrical Barnstead still; the water from the still passed through a Micromax conductivity indicating recorder, which rejects water having more than one part of foreign material in 75 million parts of water. With few exceptions (one of which will be described below) all of the plasma was adminis-

tered in the 4 or 5 fold concentration, i.e., 12.5 to 16 grams of dried plasma dissolved in 40 to 50 c.c. of pyrogen-free water. Less than a minute usually is required for the process of dissolving. The addition of 250 c.c. of water would be required to bring the plasma to so-called isotonicity or to the

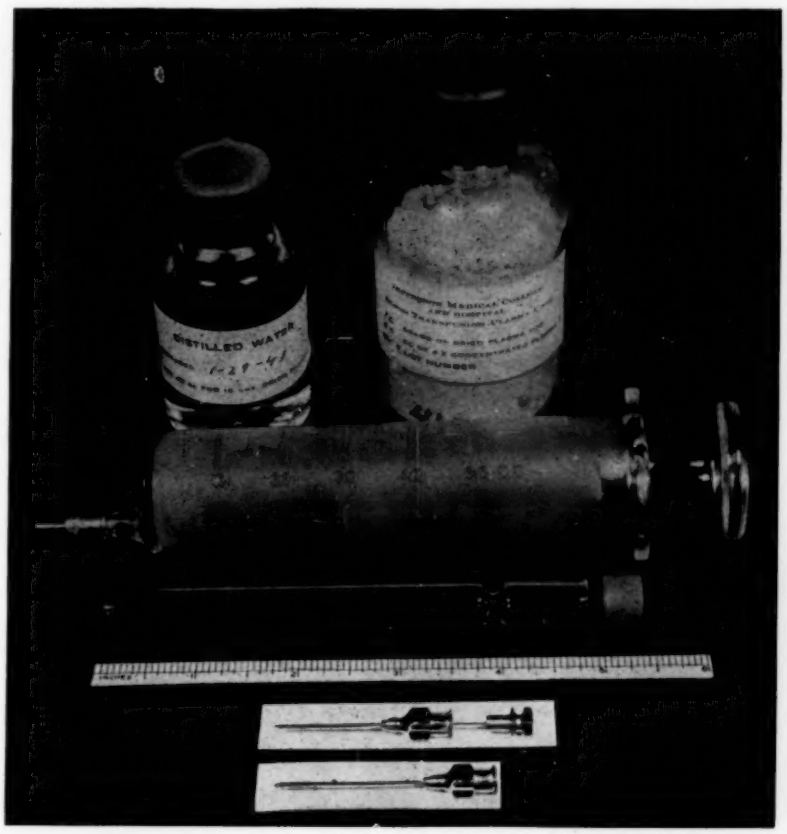

FIG. 1. The illustration shows 16 grams of dried plasma in a 120 c.c. vial, 50 c.c. of pyrogen-free distilled water in a 60 c.c. vial, a 50 c.c. syringe, a 20 gauge needle for intravenous administrations and a 20 gauge styletted needle for intrasternal administrations (18 gauge styletted needles are better for the latter because 4 fold to 5 fold concentrated plasma is quite viscid) with test tube container and rubber cap. The combined weight of the above articles securely wrapped in corduroy cardboard and heavy wrapping paper is one pound, and the package measures 8 by 4 by 2 inches. Unwrapping such a package, dissolving the plasma and administering it, can require as little as 5 minutes of time. It can be administered in fox holes or on rolling ships or ambulances. (Since our armed forces are well-supplied with medical equipment only the 120 c.c. vial with plasma need be shipped from this country. It weighs 160 grams.)

original fluid state. The pH of restored plasma without the addition of CO_2 varies between 8.1 and 9.3, but with the addition into the sealed bottle, before water is added, of 120 c.c. of CO_2 (the amount removed in the process of drying) the pH is brought down to 6.8–7.8. Those vials in which the air was replaced with CO_2 before storage did not need additional CO_2 to bring

the pH to 6.8–7.8. The CO_2 was obtained from small cylinders which can be found in any anesthetist's equipment.

	pH	Prothrombin (% of normal)
1. On collection from three donors. Fresh citrated blood	7.8	100
2. Four days later after separating and pooling of plasma (fluid)	7.8	75
3. Six days later after drying and restoring to original tonicity, with		
(a) H_2O	9.2	27
(b) H_2O and CO_2	7.5	43
4. Six weeks and one year after restoring dried plasma to fluid state (original tonicity) with		
(a) H_2O	9.0	30
(b) H_2O and CO_2	7.4	33

As can be observed the prothrombin levels dropped proportionally to time of storage before drying. Prothrombin of plasma does decompose on standing in the fluid state, but decomposes very slowly, if at all, in the dried state. Very little plasma prothrombin is lost if plasma is dried within 24 hours after removal from donor and if, when it is to be used, it is restored to the fluid state with water and CO_2 (in the amounts that were removed in drying—usually 60 vols. per cent or 60 c.c. per 100 c.c. of fluid plasma).

c. Transfusion Sites. Most of the blood transfusions were administered intravenously; however, many were administered by other intra-endothelial routes; through the intrasternal or intratibial marrow cavities. The corpus cavernosum of males, a site of transfusion suggested by Strain,[8] was used only once; it was successful. In cases of severe shock, or in children, or in very fleshy patients in whom veins were not palpable, or in cases of burns where veins were mutilated or in cases (of epileptics, or on board a rolling ship or ambulance, etc.) in which motion of arms or legs could not be satisfactorily controlled the other intra-endothelial routes became necessary. We have administered blood and both concentrated and diluted plasma intrasternally with the aid of syringes or by the "drip" method. Craver [9] pointed out that the first diagnostic sternal aspiration was done by Mosler in 1876. This site has been used extensively for aspiration [10] and injection purposes [11, 12] since.

d. Reactions Following Administration of Blood or Plasma. From patients who have reactions, the following information (on mimeographed sheets) is obtained:

Card No. of

Patient.....Donor.....Date.....trans.....

Age of Patient.....Attending Physician.....Ward or Room.....

Amount of blood received.....Type of blood.....

Diagnosis of patient.....pre- or postoperative.....

Complications.....

(pregnancy, abortion, pulmonary or hepatic disorders, malignancy or previous multiple transfusions)

Type of reaction (urticaria.....Incompatibility.....chill without fever.....Chill with temperature rising so many degrees above pre-transfusion level.....

Temperature:	Before.....	Pulse:	Before.....	Resp.:	Before.....
	During.....		During.....		During.....
	After.....		After.....		After.....
	After.....*		After.....*		After.....*
	After.....*		After.....*		After.....*

Blood pressure: Before..... After.....
Time..... Time.....

Pre-transfusion findings:

Course of disease (fever-free, septic, etc.).....
Pre- or postoperative.....
Type of operation (difficult....., prolonged....., severe.....),
hemorrhage....., etc.....
Number of transfusions previously administered and date of administrations.....
.....
Had morphine or atropine been given before transfusion.....
Had patient been receiving "sulfa" drugs....., if so what was the last blood level before transfusion.....date of level.....
Was patient nervous before and during transfusion.....
Was patient in circulatory collapse.....
Condition of heart.....diagnosis.....
Conditions of lungs.....
Was there a dry cough.....
Was there difficulty in inserting the needle (pain, etc.).....
Was there "water of condensation" in tubing of transfusion set.....
How long previous to transfusion had transfusion set been sterilized.....
Was cellulose tubing used.....

Findings during transfusion:

Time of transfusion (a.m. or p.m.).....
Changes in color of skin.....
Presence of urticaria.....
Did patient shake.....
Did patient complain of chilliness.....

Laboratory data:

(a) Before transfusion—
Hgb. for several days, weeks or months previous to transfusion.....
Van den Bergh.....
Urine analysis..... pH.....
(b) After transfusion—
Time interval after reaction when temperature returned to pre-transfusion level.....
.....
Results of recrossmatch.....
Titer of blood given (Anti-A and Anti-B).....
Rh agglutinogen determination.....
Hemoglobin { before transfusion..... / immediately after transfusion..... / 24 hrs. after transfusion..... }
Spectroscopic examination of { Plasma / Urine } for { oxyhemoglobin / methemalbumin }

Urine:

Acidity of urine.....
pH.....

* In column marked "after"—indicate time in minutes or hours.

Urobilinogen level.....
Hematin crystals and casts.....
Time collected after transfusion.....

Characteristics of citrated blood administered:

How old was blood.....had it been frozen.....
Had blood stood in room long before administration.....
Amount of hemolysis.....was blood shaken violently.....
Presence of chylomicron or fat.....
Was blood free of clots and properly citrated.....

Technic of administration:

How fast was blood given, amount of blood and interval of time.....
Was metal filter plugged.....
Were other fluids or therapeutic agents being given at the same time.....
Was patient kept warm during transfusion.....

Donor:

Did donor have a 'cold' or infection or other physical dysfunctions.....
If patient was retransfused was the same donor used.....

COMMENTS:

.....
.....
.....

RESULTS

During the year there were 3,906 donors (3,808 gave approximately 500 c.c., and 98 gave approximately 250 c.c. of blood) from whom were withdrawn 3,857 bottles of blood each of approximately 500 c.c. quantities. The blood was dispensed as follows:

2,571 bottles { 2,397 transfusions of 500 c.c. each
214 transfusions of 250 c.c. each
258 transfusions averaging 130 c.c. each

2,869 transfusions

1,177 bottles from which the plasma was centrifuged or separated and then dried (Hill Adtevac process)

109 bottles destroyed or otherwise used (breakage 30, positive serologic test 71, and research 8). 1.8 per cent of the donors had positive Wassermann or Kahn tests. Although it is well known that spirochetes can not survive more than 48–72 hours in cool (35° F) citrated blood, such blood was discarded.

3,857 bottles

The 2,869 transfusions were given to 1,089 patients (897 receiving blood only and 192 receiving both blood and restored dried plasma). Three hundred fourteen patients (192 receiving both blood and restored dried plasma and 122 receiving only restored dried plasma) were given dried plasma as follows:

316 infusions of 16 gm. of dried plasma restored in 50 c.c. pyrogen-free distilled water.
344 infusions of 12.5 gm. of dried plasma restored in 40 c.c. pyrogen-free distilled water.
35 infusions of 2 to 11.5 gm. of dried plasma restored in various quantities of pyrogen-free distilled water.

695 infusions of plasma. Practically all of the plasma infusions were administered as 4 or 5 fold concentrated plasma or the dry product restored to one-fourth or one-fifth of its original fluid volume.*

Two hundred and sixty-one units (16 gm. each) of plasma were dispensed elsewhere and 200 units were on hand at the close of the year, accounting for the approximate 1,150 units produced during the year. A few units were used for research purposes.

Blood Transfusions

The transfusions, arranged according to International typing nomenclature, to quantity per day and to services of the hospital, follow:

Type of Blood	No. of Transfusions
"O"	1,308
"A"	1,067
"B"	334
"AB"	160
	2,869

No. of Patients	Amount in One Day
1	2,000 c.c.
4	1,500 c.c.
2	1,250 c.c.
66	1,000 c.c.
8	750 c.c.
536	500 c.c.
214	250 c.c.
258	10 c.c. to 200 c.c.
1,089	

Services	No. of Transfusions
Priv. and semi-priv.	721
Women's Surg. Wd.	454
Men's Surg. Wd.	418
Gynec. Wd.	256
Men's Special Wd.	205
Men's Medical Wd.	205
Women's Medical Wd.	146
Maternity Wd.	189
T.B. Wd.	75
Children's Wd.	54
Urology Wd.	33
Miscellaneous	113
	2,869

The greatest quantity of blood administered to any one patient in 24 hours from this Transfusion Unit was 2,000 c.c. Most transfusionists feel that that quantity is a maximum, but when blood is needed there probably is no maximum quantity. Wiener and Pennell [13] have given 5,000 c.c. of blood to one patient in 24 hours. One patient (M. L., carcinoma of cervix) had 46 transfusions (the largest number given to any one patient), another (J. P., bleeding peptic ulcer) had 36, and another (J. B., hypoplastic anemia) had 32 of 500 c.c. each. These three patients were alive and well one year, three months, and six months respectively after the final transfusion.

Reactions to Transfusions

Total number of patients	1,089
Total number of transfusions	2,869
Total number of reactions (incompatibility, or associated with chills with or without fever, or urticaria)	94 (occurred in 74 patients)
Percentage of all reactions	3.2
Percentage of pyrogenic reactions	2.3

* By June 1, 1943 over 1200 administrations of plasma (the great majority as 4 or 5 fold) had been given; with the reaction rate less than 0.1 per cent.

The percentage of reactions is closely similar to those of other clinics.[14] There are those,[38] however, who feel that post-transfusional febrile reactions "cannot be reduced to a level lower than about 3 per cent," and that these non-specific reactions "are not caused by specific agglutinogens or antibodies, such as 'A' and 'B' substances or by isohemolysins, isoagglutinins, anti Rh substances and so on," but rather by pyrogenic substances in the intravenous apparatus or in the solutions used. Ninety-five per cent of the patients, 91 per cent of the transfusions and 100 per cent of the reactions, arranged according to diagnosis, follows (table I):

TABLE I

Diagnosis	Cases of Infections (*Includes patients with or without surgical interference*)	Medical Cases (*Cardiovas., renal dis., arthritis, cirrhosis of liver, etc.*)	Surgical Cases (*Hysterectomy, hernia, E.N.T., etc.*)	Cases of Anemias: *Prim.* (*Leukemia, purpura, etc.*)	Cases of Anemias: *Sec.* (*G.I. ulcers, fibroids, etc.*)	Cases of Malignancies (*Includes patients with or without surgical interference*)	Totals
No. of patients	251	96	413	36	33	211	1040
No. of transfusions	711	238	781	181	63	646	2620
No. of reactions	54	5	3	6	7	19	94
% of reactions	7.5	2.1	0.3	3.3	11.1	2.9	
% of pyrogenic reactions	5.6	1.6	0.1	2.7	6.3	1.9	

	No. Pts.	No. Trans.	Reactions No.	Reactions %		No. Pts.	No. Trans.	Reactions No.	Reactions %
G. I. Infections (*Appendicitis, peritonitis, cholecystitis, colitis, etc.*)	59	174	9	5.1	G. I. Malignancies	122	367	6	1.6
Resp. Infections (*Bronchiectasis, lung abscess, empyema, etc.*)	57	236	13	5.5	Resp. Malignancies	22	59	5	8.4
Gyn. Infections (*Pelvic infl. disease, infected abortions, puerperal sepsis*)	42	98	12	12.2	Gyn. Malignancies	26	99	1	1.0
	158	508	34	av. 6.6%		170	525	12	av. 2.2%

Pyrogenic reactions following transfusions arranged according to frequency and diagnosis:

Gyn. infections	12.2%
Respiratory mal.	8.4%
Second. anemias	6.3%
Respiratory inf.	5.5%
G. I. infections	5.1%

If pyrogenic reactions are due exclusively to foreign proteins such as bacteria, etc. in the equipment used for administering transfusions, one would feel that the distribution of reactions would be approximately equal regardless of diagnosis.

CASE REPORTS OF REACTIONS TO BLOOD TRANSFUSIONS (table 2)

The 94 reactions, which occurred in 74 patients, arranged according to type and diagnosis, follow:

TABLE II

Type of Reactions	Infections					Malignancies					Anemia		Medical		Surgical			Totals
	G.I.	Resp.	Gyn.	G.U.	Med.	G.I.	Resp.	Gyn.	G.U.	Misc.	Pri.	Sec.	G.I.	G.U.	G.I.	Gyn.	Neu.	
1. Chill but no elevation of temperature	2	2	1	1	1	3	1		1		1	2				1		16
Chill with fever of—																		
2. 1°	2	1	2		1	3	3				1	2	1		1			17
3. 2°	5	7	9	1	4	1	1				2	2	1	1				34
4. 3°	2	1	1			2	1				1		1					9
5. 4°		4						1			1							6
6. Urticaria	3	1	2			1				1		1					1	10
7. Incompatibility	1												1					2
Totals	15	16	15	2	6	10	6	1	1	1	6	7	4	1	1	1	1	94

a. Chills without Fever. Of the 94 reactions following transfusions of blood, little can be said of those (total of 16) in which the patients complained of chilliness without an associated elevation of temperature. Apparently no harm occurred to the patients. However, it has been noted that in several patients with fever, the temperature will become normal during the transfusion and remain normal thereafter. The following is a case in which this occurred: K. McG., acute pyelitis, had fever of 103° F. at start of the transfusion. Hemoglobin level was 55 per cent at that time. During the transfusion of 500 c.c. of citrated blood the temperature became normal, but the patient became very chilly, his teeth chattered and his arms and legs shook. Patient remained free of fever for three days. Hemoglobin level was 59 per cent, 24 hours after the transfusion.

b. Chills with Fever (Pyrogenic Reactions). Of the 66 reactions associated with various degrees of elevation of temperature, in only five instances (M. C.—bronchiectasis and myocarditis, J. H.—carcinoma of the esophagus, G. S.—acute lymphoid leukemia and J. J. and I. M.—secondary anemia due to bleeding fibroids) did reactions with hemolytic aspects occur. These were determined by an increase in urinary urobilinogen levels; no clinical jaundice or hemoglobinuria was observed in four of the cases. Despite the increase in urinary urobilinogen levels in two cases (M. C. and G. S.) an elevation of the hemoglobin levels occurred 24 and 48 hours after transfusion, over the pre-transfusion levels. None developed oliguria. All of the cases had had many transfusions previously. The case that did develop clinical jaundice follows:

I. M., with a secondary anemia due to bleeding fibroids, had type "A" blood. On 6–26–42, 500 c.c. type "O" blood were administered. This was one of the three instances of 2,869 transfusions when blood other than the type identical to that of the patient's was administered. The transfusion was started at 2:30 p.m. with temperature 99° F., pulse 86; at 4:00 p.m. temperature 99.9° F. and pulse 100; at 6:00 p.m. temperature 102.3° F. and pulse 120. There was no significant change in respiration rate or blood pressure. At 11:00 p.m. temperature was normal again. The next morn-

ing the patient was mildly but distinctly jaundiced and the urine urobilinogen level had risen from 1 : 10 to 1 : 100, bile pigments were present in urine and the hemoglobin level did not change (50 per cent before and 50 per cent 12 and 24 hours after transfusion). The urine was very 'acid' before and after transfusion. It was felt that the reaction was due to the fact that the anti-A titer of the donor's blood was 1 : 512. Klendshoj et al.[15] feel that anti-A and anti-B titers of 1 : 100 or over are very dangerous. Aubert et al.[5] do not agree that such titers are dangerous; they believe that titers over 1 : 512 may be harmful, however.

Klendshoj et al. suggest that A or B specific substance be added to bring the anti-A and anti-B titers down to 1 : 2 or thereabout before "O" blood is administered. They feel that small Blood Banks can be operated successfully on only "O" blood if A and B specific substances are used. It is not yet known whether the A and B specific substances, if given in too large doses, might be responsible for the development of dangerous antibody formation. This is not likely because the excess is probably neutralized or excreted.

An explanation for the other four hemolytic reactions could not be determined. The urine urobilinogen levels were 1 : 100, 1 : 200 and 1 : 400 (two cases), respectively.

We have, as have others,[16] observed that if cases that had had a febrile reaction (not hemolytic) following a transfusion were given more of the same blood a few hours later, no febrile reaction occurred and, furthermore, the post-transfusion hemoglobin levels rise proportionally to the total amount of blood given. Example follows,

M. C., colored female, aged 38, with diagnosis of bronchiectasis and myocarditis, had received 200 c.c. of a 500 c.c. bottle of citrated blood on February 6, 1942, when the patient developed a chill associated with an elevation of temperature to 102° F., and an increased number of râles in the chest. The transfusion was stopped; the remaining 300 c.c. of citrated blood were placed in the ice box for 16 hours, then readministered to the same patient without the occurrence of fever, without chills, and without an increase in the number of râles. The hemoglobin level just before the administration of the 200 c.c. quantity of blood was 70 per cent; five hours after the administration of the 300 c.c. quantity it was 79 per cent; and 24 hours later it was 81 per cent.

We have had many cases similar to the one just described, but we also have observed the opposite sequence of reactions, as follows:

A. P., white female, aged 34, with diagnosis of ulcerative colitis, received 250 cc. of a 500 c.c. bottle of citrated blood on March 14, 1942, without reaction. Because of that fact, the remaining 250 c.c., which had been stored in the ice box, were administered the next day. It, however, was followed by a shaking chill which was associated with an elevation of temperature to 101° F. The hemoglobin level just before the first administra-

tion of 250 c.c. of blood was 47 per cent; four hours after the second 250 c.c. quantity it was 49 per cent; and 24 hours later 55 per cent.

In both cases just mentioned, each had had many transfusions before and after these specific instances without reactions, and to the best of our opinion, no significant changes either in the citrated blood or the clinical condition of the patients could account for these febrile reactions. One might say that the first case developed an immunity, or that all of the reactive agents producing the febrile reaction were consumed during the first transfusion; and in the second case the second 250 c.c. quantity of blood had become excessively hemolyzed or altered. The only conclusion, theoretical in nature, that we could reach was that the reactions were possibly due to reactive circulating proteins of the recipient possibly derived from the food eaten or from the infected lesions present in the body. Masor and associates [17] demonstrated that in dogs harmful reactions occurred most frequently when the donor had been fed a protein or carbohydrate-protein meal and the recipient had been fasting. A week later A. P., the case last mentioned, was given 250 c.c. of a 500 c.c. bottle of citrated blood on March 24, 1942, and the remaining 250 c.c. on March 25, 1942, without reactions following either transfusion. Such "divided" transfusions have been given to many patients without reactions following either transfusion (L. H. (3–11 and 3–12), J. M. (3–14 a.m. and 3–14 p.m.), J. D. (5–14 and 5–15), H. C. H. (5–4 and 5–6), J. B. (6–11 and 6–12), and J. C. (7–24 a.m. and 7–24 p.m.), etc.).

c. Urticaria. Little need be said about the 10 cases that had urticaria. All responded satisfactorily to adrenalin. The donors had not eaten for a period of at least three hours before donating their blood. However, it is generally assumed that all cases of urticaria are due to an allergic sensitivity to the donor's blood or its contents. None of the 10 cases developed an elevation of temperature. The transfusions were not stopped when urticaria developed and the urticaria did not progress in severity, indicating that all of the reactive antibodies had been consumed or combined during the administration of the first few c.c. of donor's blood. Two hundred fifty c.c. of a 500 c.c. bottle of blood of one donor (F. K., 7–29–42) were given to a patient (A. G., gastric carcinoma) who developed severe urticaria, whereas the remaining 250 c.c. were given to another patient (H. H., abortion) within 12 hours' time of the first transfusion without the slightest evidence of an urticarial reaction.

d. Incompatibility. 1. A and B agglutinogens: There were two patients who suffered reactions due to incompatibility. One was due to sheer negligence of the ward administrator because all of the bottles were and are plainly labeled. Blood of group B was given to patient of group A. However, the patient had received but 25 c.c. of blood when this was discovered. He suffered a shaking chill with elevation of temperature but he did not develop hemoglobinuria. According to Oehlecher,[18] at least 80 c.c. of blood

must be hemolyzed before hemoglobinuria will occur in an adult. The other case of incompatibility brought out two interesting features, and follows:

R. R., 48 year old male from whom a gangrenous appendix was removed on August 20, 1941, in another hospital, was typed elsewhere as a "B" and was given 500 c.c. of "B" blood on three occasions (August 22, August 24, and August 26) without reactions. Under unusual circumstances a bottle of "B" blood from this Transfusion Unit was sent to the other hospital on September 4, 1941. (This has been the only occasion that blood has been sent outside of Jefferson Hospital or associated departments.) A non-centrifuged cross-match was watched for 10 minutes and no agglutination occurred on 'either side of the slide.' After 10 or 15 c.c. of blood had been administered, the patient developed dyspnea, hyperpnea, circulatory collapse, muscular incoördination and became irrational; he did not have headache, backache, or chills. After obtaining high titered serum it was found that the patient's blood was type "O," and that 30 minutes of time had to elapse before the cells agglutinated on re-cross-matching (slide method). The patient had built up antibodies against "B" cells following the three transfusions of "B" blood, and on September 4, 1941, the titer of the patient's serum for "B" cells was 1:1024, for "A" cells, 1:32. On September 11, 1941, serum of the patient agglutinated "B" cells in dilutions of 1:4096. The patient was discharged well on September 24, 1941.

This case illustrates that antibodies were not formed in sufficient numbers to cause a reaction after the first three transfusions. However, after a lapse of 10 days, the antibody concentration rose to dangerously high levels and some 20 days later to exceptionally high levels. The other unusual feature in this case was the delayed agglutination on cross-matching by the usual standard 'slide' technic. We have had three patients (R. E.—Cooley's anemia, R. R.—post-appendectomy, and J. H.—carcinoma of esophagus) who had delayed or retarded agglutination (slide method) on cross-matching of 11 mins., 30 mins. and 35 mins., respectively. The period of delay can be essentially eliminated by centrifuging. The Landsteiner technic is the only safe technic of cross-matching.

2. Rh agglutinogens: There are three types of Rh agglutinogens—Rh_1, Rh_2 and $Rh_{1\text{ and }2}$.[4b] In all cases that had multiple transfusions, or that were pre- or post-delivery or abortion, determinations were made for the presence or absence of the Rh agglutinogen [4b] in the red blood cells. Of the 74 patients that had reactions (94 reactions) Rh tests were made on 48 patients—all were Rh positive. Of four mothers, who delivered very jaundiced babies, three (mothers of C. D., R. R. and B. H.) were Rh negative. Only plasma was administered to these mothers post-delivery. The babies spontaneously overcame their jaundice.

The Rh antibodies that developed in the serum of R. R.'s mother were of the Rh_2 variety and the titer reached a level of 1:512 three weeks after delivery. The titer was 1:256 six months after delivery.

We had one patient (E. K.) who had purpura and had had many transfusions and who said that she had a febrile reaction every time she had a transfusion except when her mother was the donor. It was then learned that both she and her mother were Rh negative—or rather the red blood cells of the patient and her mother did not contain the Rh agglutinogen—thereby probably explaining the absence of reactions.

3. Cold agglutinins. There was one case (E. B.—rheumatic fever) that had marked concentration of cold agglutinins. At room temperature agglutination was still present in dilutions of 1 : 1,280.

Discussion of Reactions Following Blood Transfusions

The data collected from the mimeographed sheets (copies are shown in the section on technic) on all the 94 reactions could not be presented in such a short discourse and only general conclusions can be discussed. As pointed out previously, the majority of reactions occurred in the cases with infections, followed by those with malignancies and with secondary anemias.

Of the infections, the gynecological cases had the highest percentage of reactions and of the malignancies, the respiratory cases had the highest percentage of reactions. One interesting finding which may or may not have any significance was the fact that of the 94 reactions, 88 followed transfusions that were administered in the afternoons or early evenings. Since much of the interns' mornings are taken up in making rounds and in assisting in operating rooms, most medications are given in the afternoons. However, it is known that in the afternoons the temperature of the average person is highest and, too, it is known that patients with tuberculosis and other pulmonary infections have elevations of temperature in the afternoons. It may be possible that human beings are more sensitive to pyrogens in the afternoons. Probably less than 66 per cent of the 2800 transfusions were given in the afternoons.

Many transfusions were given just before, just after or during the administration of other medications. In this hospital, 0.94 per cent of patients given 5 per cent glucose and saline solutions (obtained elsewhere) develop pyrogenic reactions. Therefore, a certain percentage of reactions attributed to transfusions are due to such solutions. Other observers [14] have shown that saline and dextrose infusions are responsible for as much as 2.8 per cent of pyrogenic reactions in an average hospital. Whether these solutions contain pyrogens or are given so fast and in such quantities, that slight myocardial decompensation or pulmonary edema develops, is not known. Men with large direct transfusion experiences (as De Bakey [19] and one of us, H. W. J.) rarely encounter "speed shock"; however, in cases with poor myocardial tone all intravenous fluids should be given slowly (60 to 170 drops per minute). Riddell [20] strongly emphasizes that all transfusions should be given slowly, and states "the slower the transfusion the less likely a rigor will occur." Whitby [21] has indicated that in cases of cachexia,

cardiac disorders and respiratory embarrassment the rate of the transfusion should be between 0.5 c.c. and 1 c.c. per lb. of body weight per hour. This rate permits the circulatory system to adapt itself to the increased fluid volume.

In the majority of the pyrogenic reactions the temperature of the patient returned to the pre-transfusion levels within three hours, rarely later than 10 hours. Of course, it is well known that many patients with infectious processes have chills and fever that last two to 12 hours without transfusions or any other medication. Such may be due to lack of "resistance" (depletion of adrenalin, etc.), but more likely are due to sensitivity to some reactive foreign protein that has escaped into the blood stream. In cases with infectious and malignant processes, foreign bacterial and cellular proteins circulate; in obstetrical patients, fetal foreign proteins circulate; in post-operative cases in which many small vessels are thrombosed, foreign proteins of clotted blood circulate; after eating food, foreign 'food' proteins circulate. Also, bacterial or fungal foreign proteins present in unclean tubing or "old" distilled water, or sterilized denaturated blood in unclean needles or bottles can be injected during a transfusion. Since most pyrogenic reactions are very similar, if not identical, with those seen following serum shock, foreign proteins are probably the most likely responsible agents in post-transfusion febrile reactions. Whitby [21] states, "simple pyrexial reactions are most commonly due to foreign protein, dead bacteria, disintegrated or intact and living but non-pathogenic bacteria; all of these may be found in improperly prepared or stale distilled water, improperly prepared solutions and dirty apparatus."

To reduce the percentage of post-transfusion reactions, the following cautions might be mentioned:

1. In typing blood, use high titered typing sera (which can be prepared [22]) and be aware that perhaps 25 per cent of such sera have high concentrations of hemolysins. Use the centrifuge-Landsteiner technic. Type for subgroups A_2 and A_3.

2. In cross-matching use the centrifuge. If the slide technic is used, wait 30 minutes or more to avoid delayed or retarded agglutination. If "O" blood is used it is probably wise to add A and B specific substances to bring the anti-A and anti-B titers below dangerous levels.[15] Homologous blood is safer.[5]

3. In all post-partum or abortion cases or cases that have had previous transfusions determine the presence or absence of the Rh agglutinogen in the red blood cells of the patient. If Rh negative, use Rh negative donors. (O Rh neg., A Rh neg., B Rh neg. and AB Rh neg.)

4. Use fasting donors who are without infections, such as infected teeth, tonsils, sinuses, fistulas, etc., and are free of syphilis, malaria, filariasis, influenza, etc.

5. Use meticulously clean apparatus. Brush inside of all tubing with weak sodium hydroxide solution. Clean needles, especially inside of hilt, with swabs dipped in hydrogen peroxide. Rinse all apparatus with pyrogen-free water and sterilize immediately after rinsing, to avoid possibility of bacterial or fungal growth. All solutions should be prepared from freshly distilled pyrogen-free water. Cellulose tubing (Hospital Liquids Incorporated) has proved to be a very satisfactory agent in administering blood. It is discarded after once used. Properly prepared it is free of pyrogens.

6. Use only well citrated and filtered (metal filters are preferable) blood. Do not store for more than 4 to 10 days. Keep blood cold and at a constant temperature (35° F). Low temperatures retard the clotting mechanism and prolong the life of red blood cells. Administer blood cold. Do not shake blood. Have pressure in bottles containing blood, near atmospheric pressure during storage.

7. In the technic of administering transfusions, preferably have urine of patient alkaline. However, Brainard [23] has shown that pyrogenic reactions occurred even if urine is alkaline. It is preferable to give a sedative or morphine 30 minutes before a transfusion. Have adrenalin available. It is also preferable to administer transfusions in the mornings, and if possible when the temperature of the patient is near normal levels. If possible prepare transfusion apparatus outside of patient's room; have sharp needles and get into vein as quickly and as painlessly as possible. Use pyrogen-free solutions for all intravenous injections. Except in emergencies it is preferable to give blood slowly, i.e., 1 c.c. per lb. per hour. Dosage of blood depends upon many conditions:

1. Degree of anemia (hemoglobin and hematocrit levels)
2. Degree of shock (plasma protein levels, etc.)
3. Level of blood pressure
4. Pulse and respiratory rate
5. Existence of myocardial and respiratory damage.

One should give that quantity of blood that will improve and maintain the blood pressure readings, and the quality and rate of the pulse to near-normal levels associated with a return of normal color of skin, etc. Massive transfusions (5,000 c.c. or more in 24 hours) are often required under war conditions. Clinical observation must be constant and critical, to determine adequate dosage.

No one knows why a transfusion is considered "a pint" except that "a pint of blood" can usually be removed from a normal person without harm. Marriott and Kekwick [24] have devised a fairly reliable guide for dosage of blood as follows:

$$\frac{\%\text{ of rise of hgb. required}}{100} \times \text{Patient's normal blood vol. in c.c.} = \text{The vol. of blood in c.c. to be transfused.}$$

There are approximately 40 c.c. of blood per pound of body weight in the normal individual. Example: 120 lb. man with hemoglobin level of 50 per cent requires a hemoglobin level of 70 per cent—$20/100 \times (120 \times 40) = 960$ c.c. of blood to be transfused in order to raise the individual's hemoglobin level to 70 per cent.

It probably never will be possible to prevent the pyrogenic reactions, following transfusions which may be due to fetal, malignant, nutrient (food), cellular, or bacterial foreign proteins circulating in the patient. However, it is possible to give blood without reacting agglutinogens or agglutinins. Such blood can be prepared in three ways:

1. Place "O" Rh negative red blood cells in "AB" plasma.[25]
2. Place "O" Rh negative red blood cells into pooled plasma.
3. To each of 500 c.c. of "O" Rh negative blood add A and B specific substance (25 mg. and 10 mg. respectively).[15]

Plasma Infusions

One thousand one hundred seventy-seven "outdated" bottles of blood (611,295 c.c) were centrifuged or separated and the plasma (295,930 c.c.) was removed.

This liquid plasma had the following characteristics:

Age	10 to 14 days old (after withdrawal from donors).
Hemoglobin	60 to 150 mg. per cent.
Solids	7.9 to 8.4 gm./100 c.c.
Total Protein	5.4 to 7.1 gm./100 c.c.
Fibrinogen	.21 to .34 gm./100 c.c.
Prothrombin	40 per cent to 80 per cent (per cent of normal blood immediately drawn from vein).

The liquid plasma was frozen in large glass ampoules and by the "Adtevac process" 18,219 grams of dried plasma were obtained (or 1 gram of dried plasma for each 16.2 c.c. of liquid plasma). The moisture content of the dried plasma varied from 0.3 to 1.0 per cent—the majority less than 0.5 per cent. When the dried plasma was restored to the original volume with distilled water, the pH varied from 8.1 to 9.3 and the prothrombin from 0 per cent to 27 per cent. If, however, CO_2 gas was injected into the rubber-stoppered vial before restoration to the fluid state the pH dropped to 6.8–8.0 and the prothrombin varied from 30 per cent to 50 per cent (see technic). The clotting time of restored plasma with water alone varied between 9 and 30 minutes; with water and CO_2—three to nine minutes.

The dried plasma was stored in paraffined rubber-stoppered glass vials of 120 c.c. capacity under vacuum or the air replaced by CO_2. After 12 months under these conditions the restored plasma had the same characteristics as those just described. About 1 gram of sodium citrate (the amount used to citrate the blood on withdrawal) was present in each 12.5 or 16 gram vial of plasma.

Sixteen grams of dried plasma restored to fluidity with 50 c.c. of distilled water (5 fold concentrated), given intravenously, will almost always cause a rise in blood pressure.[26, 27, 28] Of 68 patients with various diagnoses, the blood pressure rose (from 10 to 50 mm. Hg systolic and 5 to 30 mm. Hg diastolic) in 56, within 15 to 45 minutes after administration of the concentrated plasma. In the other 12 the blood pressure was unchanged. In 14 patients (postoperative shock, nephrosis, nephritis and ulcerative colitis), the blood pressure, the per cent of hemoglobin, the hematocrit and the plasma specific gravity were determined before, and 15 minutes and 1 hour after the administration of 50 c.c. of 5 fold concentrated plasma on 63 occasions. Only in three instances did the blood pressure fail to rise and in only three instances did the hematocrit and hemoglobin levels fail to become lower. The plasma specific gravity levels rose in all but 11 instances. Similar findings have been reported by Hill et al.[4d] A typical example is seen in table 3.

TABLE III

Effect of Administration of Concentrated Plasma (intrasternally) (16 grams dried plasma dissolved in 50 c.c. water and administered 30 minutes after hemicolectomy).
Age of patient—57 years

	Blood Pressure	Hemoglobin (gm.)	Hematocrit %	Specific Gravity of Patient's Plasma
Before administration of plasma	98/52	10.1	37.0	1.0271
15 minutes after administration of plasma	125/62	9.7	35.4	1.0274
1 hour after administration of plasma	134/84	9.7	35.6	1.0280

Prothrombin levels were not changed in 12 patients after administration of 16 grams of plasma whether restored with water alone or with water and CO_2

As stated above, 4 and 5 fold concentrated plasma has been given intravenously most frequently, but in dozens of cases it has been administered intrasternally, essentially in cases of emergency when veins could not be found. Either concentrated or diluted plasma may be given most satisfactorily by this route.[42] In our experience of administering over 1200 infusions of concentrated plasma we find that severely dehydrated patients (exsanguinating hemorrhages in cases of ectopic pregnancy, placenta previa, post operation, etc.) apparently overcome shock more satisfactorily and quickly when first given concentrated plasma followed by saline infusions than when given isotonic plasma alone. Time is probably the significant factor.

Since the work of Post and Patek [47] who determined that 3.1 grams of albumin per 100 c.c. of plasma is the critical level for the formation of ascites in cases of cirrhosis of the liver, we have administered concentrated plasma to several patients with ascites (associated with cirrhosis of the liver) and with plasma albumin levels below 3.1 grams and have had startlingly encouraging results, such as complete disappearance of ascites. Such therapy, at the

present time, can only be considered as replacement therapy. The permanent effects are as yet unknown.

Reactions to Plasma Infusions with Case Reports. Six hundred ninety-five infusions of plasma were administered to 314 patients during the year. Well over 95 per cent of this number of infusions were given as the 4 or 5 fold concentrated solution. Only six reactions were observed in three patients.

J. S., a 44 year old male, was operated on for perforated duodenal ulcer on January 9, 1942 on which day he also received 25 grams of plasma (5 fold concentrated) without reaction. On January 17, 1942 and on January 20, 1942, 12.5 grams were given without reactions. On January 21, 1942, the patient developed slight dyspnea, slight tingling of fingers, and became beet red in color, associated with 1° rise in temperature and slight increase of pulse rate following administration of 12.5 grams restored plasma. This was not a typical reaction seen following transfusions. Fifty c.c. of 4 per cent sodium citrate were given intravenously and the same peculiar reaction occurred. On January 27, 1942 the patient received 16 grams of plasma without a reaction.

The reaction could not be attributed to the plasma in this case but rather to the citrate in the plasma.

D. L., a 9 year old male in the nephrotic stage of chronic nephritis, had generalized edema. On April 3 and April 14, 1942, by abdominal taps, 2,600 c.c. and 3,000 c.c. of ascitic fluid were removed. Sixteen grams of plasma were given on May 11, on May 14, on May 15, and on May 17, 1942 without reactions. Dr. K. Paschkis and one of us (L. A. E.) decided to administer antuitrin G in addition to the plasma in the hope that the proteins might be better retained.

On May 20, 1942, 16 grams of plasma were given intravenously with 5 c.c. of antuitrin G given intramuscularly. A pyrogenic reaction followed—temperature rose to 102° F. The same medications were given on May 21, 1942 followed by a severe pyrogenic reaction; temperature rose to 104° F. The same medication was given May 22, 1942 followed by a reaction and a temperature rise to 101° F. On May 23, 1942, 16 grams of plasma were given alone and no reaction occurred. On May 24, 1942, following both plasma and antuitrin, a reaction occurred. From that time on plasma and antuitrin were given on alternate days without reactions. The patient was discharged edema-free on June 10, 1942. Because of the excellent clinical results the same procedure was tried on two other cases of nephritis with edema (M. B. and E. H.). In neither case did reactions occur following simultaneous administrations of both plasma and antuitrin G. Excellent clinical results were obtained in all of the patients. In fact all three patients have been in clinical remissions for over eight months (February 1, 1943).

These four reactions can not be attributed to plasma but to the combination of plasma infusions and antuitrin injections. The explanation for the

reactions in the first case is most unclear since the other two patients did not develop reactions.

N. D., a 42 year old male, was operated upon for gangrenous appendix and streptococcic peritonitis on June 27, 1942. On the eighth postoperative day, 16 grams of plasma restored in 200 c.c. of distilled water were poured into 1,000 c.c. of saline and administered intravenously without reaction. When this procedure was repeated on the next day the patient developed a severe shaking chill with a 4° rise in temperature.

This reaction might have been due to the saline; or the plasma proteins with the saline might have formed a proteinate salt to which the patient was sensitive, or the intravascular osmotic pressure may have been raised to such levels as to absorb some bacterial proteins into the blood stream. We recommend that plasma always be given in the concentrated form unless the patient is definitely dehydrated.

Discussion of Reactions. Of the six reactions only the last one might be attributed to the plasma per se. So out of 695 administrations there was one reaction—a reaction rate of 0.14 per cent. This percentage is even lower than that of Hill et al.[7] We have noted that some patients complain of vasospasm of the injected vein when injecting 5 fold concentrated plasma with the pH above 8.5. By adding CO_2, which brings pH of the plasma down to 7.5 or less, vasospasms usually cease.

Discussion of Plasma. Albumin,[29] serum [30, 31] and plasma are available either in the liquid or desiccated state and all are satisfactory therapeutic agents for:

1. Overcoming shock
2. Restoring blood volume
3. Overcoming protein deficiency,[32] and
4. The constitutional treatment of burns.

a. *Albumin.* Cohn [29] precipitates albumin from human plasma by use of alcohol-water mixtures. Nearly two-thirds of human plasma is made up of albumin, which is responsible for the great majority of the osmotic pressure exerted by blood. (Albumin has a smaller molecular size than globulin.) Albumin may be desiccated and restored to a 4 or 5 fold concentrated solution or to the original fluid (isotonic) state by buffered saline. Four or 5 fold concentrated plasma will give the same experimental and clinical results that 4 or 5 fold concentrated albumin does [33, 34] and such plasma is much cheaper. Janeway [40] feels that it will be possible in the future to purify bovine albumin so as to be in general use since it seems to be a relatively poor antigen in man. Others [35, 36] are trying to despeciate horse albumin successfully. However, if non-human albumin fails to become a commercial product there is an unlimited amount of human cadaver blood at all undertaking establishments from which human albumin could be commercially produced. Denaturation of the albumin should not be marked, because the Russians have been using cadaver blood successfully for transfusions for years.

b. *Serum.* There is considerable discussion as to the superiority of serum versus plasma in the treatment of shock. If properly prepared both are very effective. However, serum does not contain fibrinogen, beta globulin, prothrombin, etc., but does contain many breakdown products which appear when blood clots, including possibly denaturated proteins which may have antibody-forming potentialities. Since serum has no particular advantage over plasma, our laboratory has concentrated its efforts on plasma. Of course, allowing the blood to clot after withdrawal does not permit its use for transfusions. Our experience has been limited to the use of restored dried serum in 4 or 5 fold concentrated solutions; however, we have used it in several cases with satisfaction. It can be used in most instances wherever plasma is indicated.

c. *Plasma.* Sturgis [37] said that ultimately dried plasma will be the agent universally used in the treatment of shock.

Plasma is usually a by-product or can be prepared from "out-dated" blood banks. The plasma can be removed from the red blood cells by centrifugation, aspiration or separation. If specimens of *blood* are pooled (10 parts group "O" blood to one of "AB" and one part each of "A" and "B" [28]) before the plasma is removed, the titers of the anti-A and anti-B agglutinins of the resulting plasma are usually reduced to extremely low levels, but if the various specimens of *plasma* are pooled the titers rarely get above 1:20 for either anti-A or anti-B.[38] Aubert et al.[39] have shown that although 99 per cent of the A and B specific substances exist in the red blood cells, 1 per cent of these substances exist in the plasma, which helps to explain how pooling of *plasma* can reduce the titer of the anti-A and anti-B agglutinins. Aubert et al.[5] have also shown that there is little danger of dangerous reactions even if these titers are as high as 1:512. No typing or crossmatching is necessary when pooled plasma is given—neither are skin tests needed or indicated.

Plasma can be made available in many ways such as:

1. *Isotonic Plasma Diluted with Equal Parts of Saline.* White et al.[40] feel that such a mixture is valuable in markedly dehydrated patients who are in mild shock. Concentration of urine usually gives some clue to the degree of dehydration (if kidneys have not been damaged or if patient has not lost significant quantities of salts); and most authors feel that specific gravity values above 1.012 indicate degrees of dehydration.

Such diluted plasma may be stored at room temperature or at 35° F. but there is always the danger of contamination.

2. *Isotonic Plasma.* If liquid plasma is stored at room temperature or at 35° F., flocculation, contamination and autolysis with denaturation of proteins can occur. Heath and Province [41] have clearly shown that they could not recommend merthiolate or "sulfa" drugs for the preservation of stored liquid plasma, and flocculation is a serious disadvantage, too.

3. *Frozen Plasma.* The necessity of low temperature ice boxes, the time required for thawing (30 minutes for 500 c.c.) and the serious clinical con-

sequences of thawing too rapidly are distinct disadvantages associated with the use of frozen plasma.

4. *Dried Plasma.* It is the most practical form of plasma. It is clinically as effective as dried albumin and cheaper.

a. It can be stored at room temperature for years.

b. It is compact and easily transported. Sixteen grams of dried plasma (the amount obtained from 500 c.c. of blood) takes up less space than that taken up by two golf balls. A 120 c.c. vial (see figure 1) which is 4.5 inches tall and two inches in diameter, and which contains 16 grams of plasma weighs approximately 160 grams. The plasma, a 50 c.c. vial of distilled water, and a 50 c.c. syringe with needles placed in a firm mailing tube weigh 16 oz. (1 lb.). A package wrapped securely in corduroy cardboard and heavy wrapping paper measures approximately 8 by 4 by 2 inches. To most of our armed forces, only plasma need be shipped because medical supplies and freshly distilled water are available at all except the front line aid stations. Frequently newspaper photographs taken at the battle fronts show wounded men receiving plasma by old-fashioned drip bottles hanging from trees, etc., and long, unwieldy tubing. This can be eliminated by administering the same quantity of plasma quickly and conveniently in the concentrated form with a syringe.

c. It has flash solubility. Sixteen grams of dried plasma will dissolve in 50 c.c. of water in one minute of time, making 4 or 5 fold concentrated plasma. Two hundred fifty c.c. of water would be required to restore that quantity of plasma to its original volume.

d. The restored plasma is not altered significantly in any known way. Scudder [46] after making electrophoretic studies feels that plasma dried from the frozen state (Adtevac and others) is superior to those in which heat is used during desiccation. If CO_2 is added to plasma before restoration to fluid state very little prothrombin is lost (see technic). Prothrombin is not an important factor in treatment of shock anyway.

	Fluid Plasma (citrated)	Same plasma dried and restored to original volume with distilled water	
		24 hrs. later	6 mos. later
Total Protein (grams per 100 c.c.)	6.0	5.8	6.0
Albumin (grams per 100 c.c.)	4.2	3.9	
Globulin (grams per 100 c.c.)	1.9	1.6	
Fibrinogen (grams per 100 c.c.)	.28	.27	.24
Hemoglobin (mg. per cent)	25.0	25.0	25.0
Clotting time (minutes) upon recalcification	5.0	10.0	10.0

e. Dried plasma can be restored to any concentration desired, 10 fold, 5 fold, 4 fold, 2 fold, isotonic or diluted (with saline), etc. Ten fold is used in cases of nephrosis, 4 fold in shock and isotonic and diluted in dehydrated

patients (urine specific gravity 1.030 or so) requiring increased fluid volume as well as blood proteins. In patients with severe shock concentrated plasma should be used first (so that both interstitial and intracellular fluids are returned to the blood stream) and continued at least until the blood pressure is restored to near normal levels, then isotonic or even diluted plasma could be given. Of course, each case of shock is a law unto itself, and must be treated accordingly.

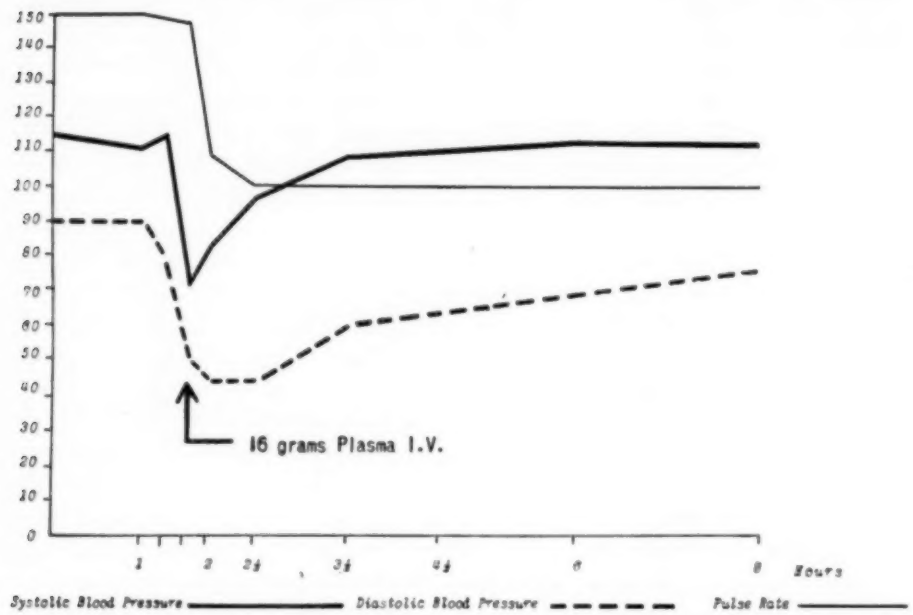

FIG. 2. Changes in systolic and diastolic blood pressure levels and pulse rate in a case of post partum shock following administration (intravenously) of *concentrated plasma* (16 grams in 50 c.c. distilled water).

f. Restored dried plasma is easily administered in any concentration. It does not require typing since it is made by the desiccation of pooled liquid plasma. Four fold concentrated plasma (dried plasma restored to one-fourth its original fluid volume) can be given intravenously or by other intraendothelial routes (see technic). To give it intrasternally insert a styletted needle (18 or 20 gauge, one inch long—an ordinary spinal puncture needle shortened to one inch in length) into the midline of the sternum at the level of the second interspace, point of needle directed cephalically at a 45° angle.[42] With aid of a 50 c.c. syringe, "one pint of blood" proteins can be given within 5 to 10 minutes, by this route. When plasma has to be given on a rolling battleship, in a fox hole, or in an ambulance, one can not resort to long rubber tubes and dripping bottles. In well over 1,200 administrations of 4 fold concentrated plasma we have never needed to filter concentrated plasma before administration.

g. Hemodilution followed the single injection of 50 c.c. of 4 fold concentrated plasma in 60 of 63 administrations. The blood pressure almost invariably rises following the administration of concentrated plasma either intravenously or intrasternally (see figures 2 and 3). The effects just described occur just as rapidly following administration intrasternally as intravenously.

h. Reactions are few, following administration of concentrated restored plasma. In 695 administrations the reaction rate was 0.14 per cent. Hill [7] likewise had less than 1 per cent reactions in his series.

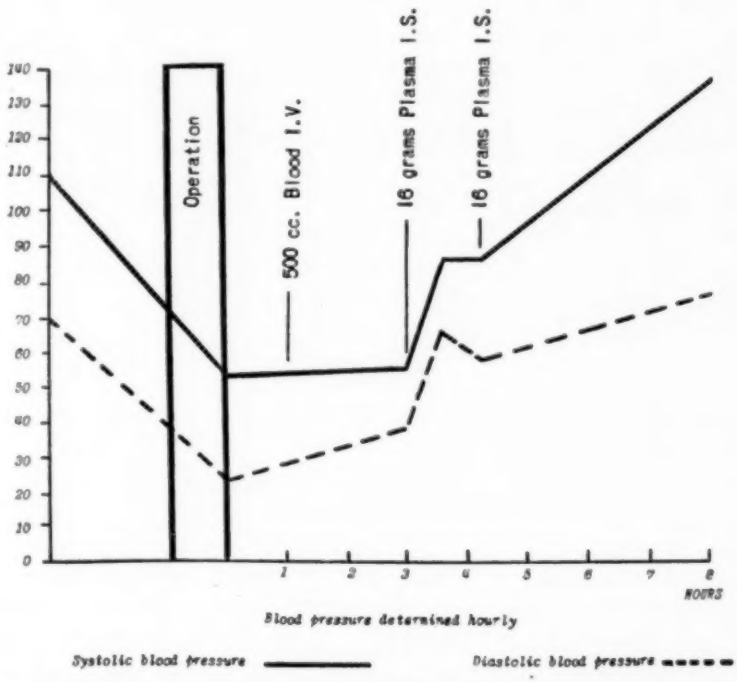

FIG. 3. Postoperative (esophagogastrostomy) changes in the systolic and diastolic blood pressure levels following administration (intrasternally) of *concentrated plasma* (16 grams in 50 c.c. distilled water). No other medication given during this period.

If animal plasma or albumin can ever be treated so as to be made non-antigenic,[46] or if human cadaver plasma or albumin becomes available commercially, most plasma banks will be eliminated. Commercial houses will readily take over such functions including the production of artificial antibodies,[43] which seems to be a distinct possibility in the future.

The Blood Transfusion-Plasma Unit dispenses many other intravenous fluids besides blood, plasma and serum, such as (1) amino acids for cases of malnutrition, hypoproteinemia, etc., (2) radioactive phosphorus, for cases of leukemia [44] and polycythemia,[45] (3) solutions of gelatin for cases of shock (if the pyrogenic substances in gelatin can be removed, it may become

a cheap and satisfactory agent in shock), (4) solutions of chlorophyll in cases of septicemia (the solutions used were ineffective in the cases of subacute bacterial endocarditis that we treated), (5) saline solutions containing alcohol and the vitamin B complex, (6) ascitic fluid, etc.; and also performs hemo-irradiation (Knott technic of irradiating auto-transfusions with ultraviolet light) of blood of patients when requested.

Conclusions

1. From 3,906 donors, blood was withdrawn at the Blood Transfusion-Plasma Unit of Jefferson Hospital during the year ending July 1, 1942. The Kahn or Wassermann tests were positive in 1.8 per cent of the donors.

2. The Blood Transfusion-Plasma Unit issued 2,869 blood transfusions, 3.2 per cent of which were followed by reactions, and 695 plasma (dried) infusions, 0.14 per cent of which were followed by reactions, during the year.

3. The reactions were classified as: (1) chills without fever; (2) chills with fever; (3) urticaria, and (4) incompatibilities. The pyrogenic reactions, or chills with fever, were most frequent.

Pyrogenic reactions, following transfusions arranged according to diagnosis and frequency of occurrence, follow:

Diagnosis	% of Reaction
a. Gynecological infections	12.2
b. Respiratory malignancies	8.4
c. Secondary anemias (secondary to leukemia or hemorrhages of the uterus or stomach, etc.)	6.3
d. Respiratory infections (bronchiectasis, lung abscesses,etc.)	5.5
e. Gastrointestinal infections (appendicitis, peritonitis, etc.)	5.1
f. Misc.	

By inference it is assumed that many of the pyrogenic reactions, following transfusions, were due to circulating foreign proteins (bacterial, fetal, nutrient, or cellular) in the recipient. However, since the percentage of reactions was much lower following plasma infusions in the same or similar cases, it must also be assumed that the red blood cells of a transfused blood are the agents that react with the circulating foreign proteins of the recipient. Measures to prevent transfusion reactions have been listed and it is hoped that the use of cellulose tubing, which is a very satisfactory substitute for rubber tubing in the administration of intravenous fluids, will reduce the number of pyrogenic reactions since such tubing is used but once.

4. Sturgis said [37] dried human plasma ultimately will be the agent universally used in shock. Dried human plasma apparently is as effective clinically as dried human albumin (when these agents are restored to one-fourth of their original fluid volume) and it is cheaper. Concentrated plasma almost invariably causes hemodilution and a rise in blood pressure (see figures 2 and 3). When plasma must be given in fox holes, on a rolling battleship or ambulance, or in civilian emergencies, long rubber tubes and

"drip" bottles can not be used conveniently. But 4 or 5 fold concentrated plasma, obtained by injecting, with the aid of a 50 c.c. syringe, 40 c.c. of distilled water into a vial containing 16 grams of plasma (the amount present in a pint of blood), can be administered intravenously or intrasternally within a very few minutes' time (see figure 1). The necessary equipment for the administration of concentrated plasma easily can be carried in a coat pocket and weighs only one pound. Concentrated plasma can be given to dehydrated patients without harm.[33] Ascites (in some cases of hypoalbuminemia due to nephritis and cirrhosis of liver) has been overcome by administrations of adequate amounts of concentrated plasma. Typing, crossmatching or skin testing is not necessary.

5. Intra-endothelial routes (intrasternal, etc.), other than venous routes of administering blood or plasma, have been life-saving in our experience.

6. Since Russia has administered successfully cadaver blood for transfusions for years it is suggested that the unlimited amounts of cadaver blood available in the nations' undertaking establishments be processed for plasma or albumin (preferably dried). Although it is the opinion of Ross T. McIntire,* Surgeon General of U. S. Navy, that there might be "strong public sentiment against the utilization of any product derived from cadavers . . .," the National Research Council † is giving the suggestion some consideration.

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CHRONIC SEASICKNESS *

By Robert S. Schwab, Lieutenant Commander, MC, USNR,
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The history of seasickness is as old as that of any disease. The Romans and Greeks mention it in several of their writings, and notables such as Cicero and Caesar suffered frequently from this condition. Nelson, although he spent most of his life at sea, was a victim of seasickness most of the time. An interesting early description of large numbers of mer being sick is found in a diary of Dr. Isaac Senter [1] who was a medical officer attached to the ill-fated expedition under General Benedict Arnold which

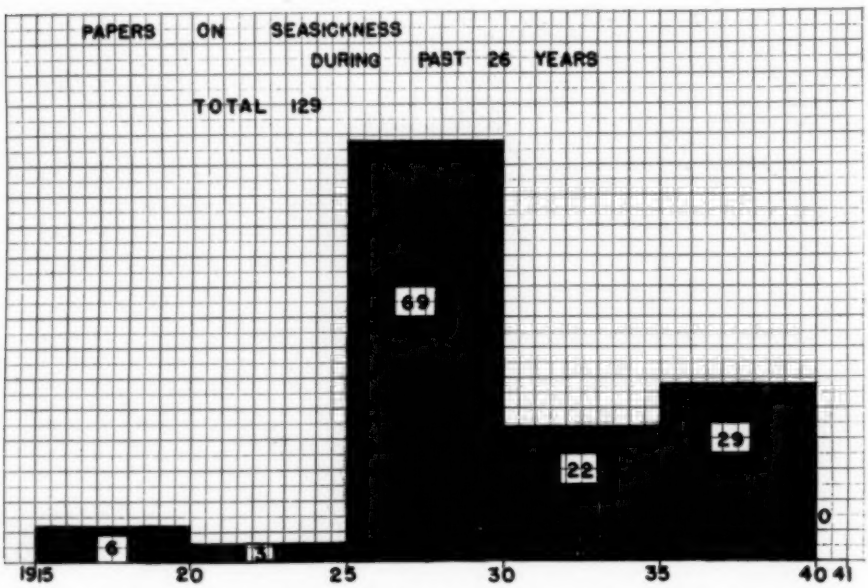

Fig. 1. A graph showing the distribution of literature on the subject of seasickness during the last 25 years.

in 1775 attempted to capture Quebec. This expedition of some 1500 men sailed in small ships from Newburyport to the mouth of the Kennebec River in Maine. Over 90 per cent of the soldiers were very seasick during the entire trip and it was noted that they considered themselves fortunate on landing at the Kennebec that they did not have an enemy to fight.

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There is a very extensive literature on the subject. It is interesting that during the lean years associated with wars and depressions in the past, little attention has been focused on this subject by the medical profession. Only nine papers were published, for example, from 1914 through 1920. In prosperous years when people travelled extensively, such as the years from 1925 to 1930, over 69 articles on this subject were published. Since 1935 there has been a marked falling off of publications in relation to this subject (figure 2). In the last 25 years over 140 articles on seasickness have ap-

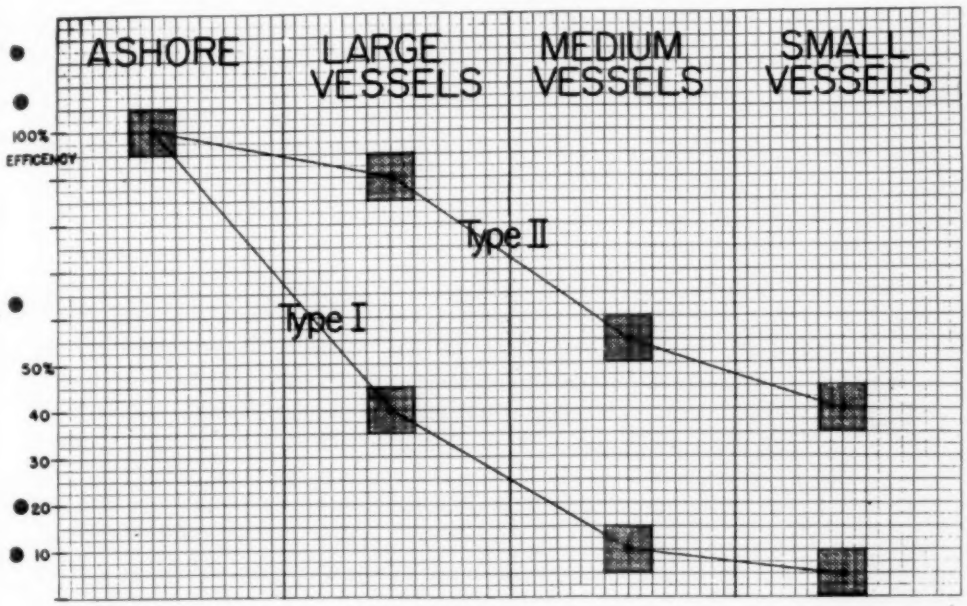

FIG. 2. Comparison of the efficiency of Type I seasickness and Type II seasickness on different size vessels.

peared in the various medical journals in the world.[2] The author has the complete bibliography of these articles in his preliminary paper of October 1942. Some of these are merely reports and personal theories by the medical officers of ships or articles written by doctors who have travelled. A few are worth reading, and a few more include careful clinical and some laboratory studies.

The general feeling is that seasickness is a complicated affair with many causes and a very complicated etiology. It is generally agreed that susceptible individuals have some hypersensitivity of the vegetative nervous system. There are those in the literature who advocate the theory that this trouble is concerned entirely with the vestibular system. Equally convincing data involve the psyche and there is evidence that the visual, olfactory and proprioceptive systems are also concerned. The wisest view is that various

types of stimuli set off the syndrome (table 2) and that different conditions in different individuals modify the general picture.

TABLE I

The order in which symptoms usually appear in seasickness.

1. Anorexia { Tobacco / Food
2. Loss of interest
   Seclusiveness
3. Salivation
   Sweating
4. Vertigo
   Nausea Headache
5. Vomiting

TABLE II

Six sources of stimuli which contribute to the development of seasickness in a subject.

A. Psychic
B. Olfactory
C. Visual
D. Vestibular
E. Gastrointestinal
F. Proprioceptive

The treatment of this disease has varied throughout the pharmacopeia with a general agreement that sedative drugs and atropine and related drugs show the most promise. One homeopathic physician, a French medical officer on a liner, believed that since seasickness was the result of a human being being thrown about on the salty ocean the natural remedy would be the ingestion of sea water which would be thrown about in his stomach. I might add the results were very discouraging to him. About three-quarters of the references to seasickness include the adage that the only sure cure is to sit under a live oak tree.

The subject as concerns the United States Navy was first brought to my attention when I came to active duty at the Naval Hospital in December 1941. Here I found to my surprise that four or five patients on the Neuro-Psychiatric Ward had been sent in because of seasickness. During the last fourteen months I have had the privilege of examining over 115 naval personnel who suffered with chronic seasickness, severe enough to bring them to the hospital either as out-patients or as ward patients.

We have found that this group is divided roughly into two main divisions, the first of which I shall call Type I. It is composed of people who get sick, not only at sea but on trains, busses, cars, elevators, swings and roller coasters, and who suffer from a variety of other motion sicknesses. These people when they get to sea become very seasick and stay sick. Their efficiency is low, they lose considerable weight and they are more or less useless on the vessel.

A second group of individuals suffers from seasickness particularly during rough weather. We call them Type II. They have no history of motion

sickness. They are able to do their work with reduced efficiency but are rarely laid up and have little weight loss. They are usually valuable men on their vessels. These two groups at first seemed quite distinct but as the number of cases became larger, it was seen that there might be an intermediate number which I have arbitrarily called Type-IA. This group gives a history of some motion sickness but gets along reasonably well in quiet water or on a big ship. Weight loss is small and efficiency is greater than in the original Type I.

We found to our surprise that 50 per cent of the subjects suffering from chronic seasickness showed abnormalities in the gastrointestinal tract. These were first picked up by barium fluoroscopy done through the coöperation of the Naval Hospital roentgenologist, Lieutenant Commander H. D. Goehring, who fortunately has had special training and experience in mucosal relief studies of the gastrointestinal tract. He found that in a man recently returned from five or six weeks of seasickness at sea, one could demonstrate the following: (1) Marked irritability of the pylorus and duodenum with resulting pyloric spasm. (2) Marked increase in gastric secretion even with fasting. (3) Some increase in the gastric rugae. (4) Loss of peristalsis. These findings persisted in some of our patients for three or four weeks, gradually becoming less marked and in one patient nearly disappearing after

TABLE III

Some of the more common diagnoses under which seasickness appears on entry into a naval hospital.

1. Psychoneurosis
2. Gastric neurosis
3. Gastric ulcer
4. Gastritis
5. Headache
6. Sinus trouble
7. Deviated septum
8. Appendicitis
9. Back strain
10. Syncope

three months.[3] In 15 of our cases we have checked the barium findings with gastroscopic examination through the coöperation of Dr. Edward Benedict of the Massachusetts General Hospital. He has found, in this group, evidence of mild, chronic superficial gastritis. The significance of these findings is not absolutely clear to us at this time, but they do show that this disease has its pathologic lesions like any other condition met in medicine, and it behooves us to study further the causes and the treatment for this condition.

Another feature of seasickness is the many diagnoses which mask the actual incidence of this state. The reason for this is clear if one remembers that being seasick is considered by most of us as something of a weakness, and by some as a disgrace. Therefore, medical officers and pharmacist's mates out of kindness or other motive will give to the seasick sailor one of the diagnoses seen in table 3. We have seen one or two patients whose sea-

sickness was severe enough to cause abdominal pain which persisted and which resulted in their being sent to a hospital and operated on for appendicitis, thus creating in my mind the syndrome of the seasick appendix.

A most interesting complication in this group is a psychoneurosis. This warrants a more detailed study. We have found, for example, that 74 per cent of the Type I individuals show neurotic trends of one sort or another, such as an easily upset stomach, a tendency to nausea and vomiting from unpleasant sights, a labile vegetative system so that syncope is common, a history of odd dizzy attacks and so forth. A number of these people, however, go through their early life without any serious psychiatric complication or illness in spite of these trends. One could say very definitely that they were vulnerable individuals with this history of being made sick in a variety of ways when exposed to motion. In the past, however, their difficulty has been taken care of by the simple method of avoiding or leaving the conveyance which made them ill. They enter the Navy, impelled to join by natural patriotic emotion, get along reasonably well at the training station, and find themselves assigned to a small ship such as a destroyer or a mine sweeper. If this happens to occur in the North Atlantic in the fall, winter or spring when it is rough, they experience seasickness the first time the vessel leaves the wharf. Now they are unable to leave the source of their disturbance, sometimes for as long as three weeks, and individuals of this type lie in their bunks vomiting, losing weight, and being very, very miserable. They are sometimes criticized or teased by their fellow sailors or officers for not overcoming this disability by will power. At any rate, they feel discouraged and inadequate, and the uselessness of their life on the ship is very obvious to them. When they finally are sent into the hospital because of the failure of the condition to disappear, whether it is under the diagnosis of gastric ulcer or frank seasickness, they now have developed definite psychoneurosis. The very thought of returning to that ship or to sea duty in general causes a host of conditioned reflexes to appear. These individuals, in an effort to prevent their return to life at sea, usually do one of three things:

1. A few with lowered appreciation of the seriousness of their offense run away.

2. A large number develop chronic complaints in the hospital not related to seasickness, such as backache, headache, stomach ache, anorexia and apprehensions of all sorts. These symptoms increase in intensity and frequency as the day of return to duty approaches. These symptoms are real and disturb the patient's equilibrium even when he is on leave. We have observed such subjects who were unable to make the usual adjustment when they went home, being sick at the family table, unable to sleep, and a few cases of psychic impotence have been brought to my attention which never existed previously.

3. The third group, small in number, simply break down in a fear reaction, sometimes tearful, sometimes belligerent, and say they cannot under

any circumstances return to sea. They plead a shore job, a transfer to the army.

We have tried recommending larger vessels, and even shore duty, for many of these individuals when they were sent back to duty, but the threat and possibility of being sent back to sea on a smaller ship is ever present and the neurotic symptoms persist. Sooner or later these individuals are sent back to the hospital and in our experience have to be surveyed out of the Navy.

Example 1. A 21 year old farmer from one of the middle western states joined the Navy in May 1942. He had never been on a ship of any description before in his life. He gave a history of being sick in automobiles, trains, busses, swings and roller coasters. He would vomit or feel nauseated by unpleasant smells or sights. There was a history of "nervous stomach" in his family. He himself had no previous gastrointestinal trouble except that induced by motion. He had gone through high school and had not had any obvious psychiatric disturbance. After high school he obtained a job on a farm and began to have occasional headaches when he worked too hard. Several times during one year he had mild dizzy spells and fainted twice from emotional disturbances. He was very upset over a love affair going wrong, after which he had nothing to do with girls and was seclusive for nearly a year. After joining the Navy he did well at the training station and was assigned to a destroyer. He became seasick as soon as the vessel left the wharf, being overcome with dizziness and vomiting so that he had to lie in his bunk. During the entire trip of 11 days he was unable to get on his feet and lost 13 pounds. Several times during the last three days of the trip the medical officer noted that he cried when interviewed and was very discouraged and unhappy. The ship made two more trips with the patient with the same results. At the end of the third trip the patient noted some blood-stained vomitus and became conscious of a pain in his stomach. There was marked exaggeration of his symptoms, and as a result of this he was sent to the hospital with a diagnosis of acute gastritis. After a fortnight's stay in the hospital with study on the wards, he was given 10 days leave. He found when he got home that he was very nervous, and he had disturbing dreams of being seasick in rough weather so that sleep was difficult. On three occasions he vomited at the family table, something that he had never done before. He had no inclination to meet his old friends and remained indoors most of the time during his leave. He reported that he cried most of the night before leaving for his station. When the decision was being made in regard to his disposal he developed pain in his back and a limp which was obviously hysterical. These all disappeared and his condition improved considerably when he was finally told that he would be surveyed out of the service and sent home.

The patients suffering from marked constitutional susceptibility to motion sickness, i.e., Type I, who do not show the neurotic symptoms mentioned above and who seem like valuable men to the service such as a doctor or radio engineer, signal man, etc., after a medical survey have been recommended for shore positions and have done well, of course, when they were thus assigned.

Example 2. A radio mechanic coming from the eastern seaboard graduated from high school and joined the Navy in 1940. He gave a history of susceptibility to motion sickness such as cars, trains, busses, swings, etc. There was no history of a neurosis in this case at any time in his past. His first six months in the Navy were

on shore. There was a brief trip on a transport lasting two weeks during which time he was sick eight days. He then was sent to a special school for three months and assigned to a destroyer where he was sick approximately 80 per cent of the time. He was, however, able to stand most of his watches in spite of his seasickness, although he lost a good deal of weight and his efficiency was considerably reduced. He was keenly interested in remaining in the service if he could avoid the difficulty of a small boat existence. In the hospital he was an obviously normal person of considerable value to the service. He was finally assigned to a shore position and is doing very well in this capacity.

TABLE IV

The two types of chronic seasickness compared as to the presence of motion sickness and efficiency

	Type I	Type II
Number of cases	51	55
Motion sickness	Yes	No
Efficiency	0–20	40–60
Weight loss	Marked	Slight
Disposal	(Shore or Discharge)	(Larger Ship and Treatment)

TABLE V

Clinical findings in the two types of seasickness compared. Note the exceedingly high percentage of neurotic individuals in Type I

	Type I	Type II
Number of cases	51	55
Neurotic	74%	24%
Fainters—dizzy spells	57%	14%
Gastrointestinal history	72%	8%
No neurotic G.I. or syncope history	17%	65%
Abnormal G.I. series	60%	30%
Abnormal gastroscope	30%	10%

These individuals who do not develop psychoneurosis and whose recovery from seasickness is rapid often can be sent back to sea on a larger ship or greatly helped by one of the usual drugs. I have had follow-up reports on eight subjects who have readjusted by the development of tolerance to sea duty. Three of these have remained on the same ship, i.e., destroyers; five have been transferred to larger vessels with a reduction in their trouble.

Example 3. A 27 year old salesman with no history of motion sickness and no history of neurosis joined the Navy in June 1942. He spent two months on a cargo vessel, being sick only two days out of 60. Following this he was transferred to a small patrol craft operating in coastal waters. He was sick approximately five out of seven days and felt that he was not doing his work although he was able to stand all his watches. Some slight blood-stained vomitus brought him to the hospital. It was recommended that he be assigned to a larger ship which fortunately was available. Six months later he reported by letter that he had not suffered from seasickness and was doing his work without any trouble.

The subject of efficiency of men suffering from seasickness deserves something in passing. It is obvious that a man with marked nausea, vertigo, headache, vomiting and a certain amount of apprehension and discouragement from the condition accompanying the above, is not as able a man as his

unaffected fellow. This difference in ability is not easy to measure but it involves alertness, skill, temper, resistance to infection, cold, heat, immersion and so forth. A small vessel with a crew of 100 men which has 50 of them violently seasick is not as efficient as a vessel with 100 men not affected. Therefore, this condition is not to be laughed at or disregarded, and has a very definite military bearing. We feel that the wisest way to handle the situation is to try to keep out of the service those individuals suffering from chronic motion sickness in the past, and these can be picked up by a questionnaire. Those that are found in the service should be sent to shore jobs if their abilities warrant their retention in the service. This is particularly true of a man who has had considerable expensive training before this condition is noted. Others not suffering from motion sickness can usually develop tolerance and can be helped by some of the anti-seasick remedies.

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OCCLUSIONS OF THE ABDOMINAL AORTA: A STUDY OF 16 CASES OF SADDLE EMBOLUS AND THROMBOSIS *

By NATHANIEL E. REICH, M.D., *Brooklyn, New York*

A HIGHLY dramatic episode in medicine is a condition variously described as thrombosis or embolism of the abdominal aorta and "rider's" or "saddle" thrombus or embolism. Approximately 150 cases of obstruction of the abdominal aorta have been reported in the literature to date. In the main, these have consisted of scattered reports of from one to five cases. We have been fortunate in accumulating 16 cases over a period of five years at Kings County Hospital. Eleven of these were autopsied and two recovered by recanalization. As far as is known this is the largest group to be studied. A careful survey of these cases reveals certain facts in the etiology, age-sex distribution, diagnosis and treatment. An analysis of the causes of failure in early diagnosis is also considered.

CASE REPORTS

Case 1. F. O., white female, aged 32, was admitted with a history of sudden loss of speech of six months' duration. She had had scarlet fever at the age of nine. At 21 she developed dyspnea and palpitation and a diagnosis of mitral stenosis was made. Two years prior to admission the patient had to be digitalized because of acute cardiac failure with pulmonary edema but fibrillation continued. While at work six months previously she fell and remained unconscious for a period of 10 days, with loss of voice and right hemiplegia. Two weeks before her present admission she awoke and coughed up a large amount of blood which was attributed to pulmonary infarction.

Examination revealed marked emotional instability with aphasia. There was cardiac enlargement with a double murmur at the apex. The second pulmonic sound was accentuated and there was auricular fibrillation with occasional extrasystoles. Blood pressure was 175 mm. Hg systolic and 95 mm. diastolic. The residual right hemiplegia was attributed to embolization to the left middle cerebral artery secondary to rheumatic heart disease. Two weeks following admission she developed dyspnea with a crampy pain in the left leg which was thought due to another embolus. Seventeen days after this episode she complained of epigastric pain and had tenderness in the left upper quadrant which was thought to be the result of a splenic embolism. Three weeks later she complained of nausea, vomited 5 c.c. of dark red blood, and had slight epigastric rigidity. Two and a half months later she vomited and complained of abdominal cramps. A tender area with rigidity was noted in the right upper quadrant which was interpreted as caused by acute cholecystitis or a penetrating peptic ulcer. Medical consultants suggested either acute appendicitis or small mesenteric thrombosis. Surgical intervention was not considered feasible at any time because the patient was an extremely poor operative risk. Later that day she complained of precordial pain, vomited, became extremely weak, and finally died.

* Received for publication June 25, 1942.

From the Kings County Hospital, Service of Dr. C. H. Greene, and the L. I. College of Medicine, Dr. J. H. Crawford, Director.

Laboratory examinations included a roentgenogram of the heart which revealed a prominent pulmonic conus compatible with an underlying congenital heart lesion. Electrocardiographic study showed no axis deviation and only slight myocardial impairment. Wassermann reaction and blood cultures were negative. Terminally the blood urea rose to 135 mg. and the sugar was 84 mg. per 100 c.c. of blood. The temperature was never over 100.5° F. throughout her two year hospital stay. The urine presented clumped leukocytes and traces of albumin but no red cells terminally.

Autopsy revealed a heart weighing 210 grams; the left auricle was markedly dilated, whereas the left ventricular cavity was small, and the wall measured 1 cm. in thickness. There was a marked thickening and fusion of the mitral valve with stenosis and insufficiency. It was free of old or recent vegetations. There were no thrombi present. The intima of the aorta was bright yellow and smooth. Just below the opening of the celiac axis extending down to the external iliac arteries, the lumen of the aorta was completely occluded by a firm, red-gray, friable thrombus. This mass extended down into the smallest branches of the superior and inferior mesenteric and splenic arteries. The mass was adherent throughout to the arterial walls and varied considerably in shade from place to place. Infarctions of the proximal two-thirds of the large intestine and the entire small intestine caused them to appear dark red and lusterless. In addition, there were large infarctions of the kidneys, spleen and in the left hemisphere of the brain extending from the ependyma of the left ventricle to the tip of the occipital lobe. The latter was cystic and orange-yellow. Microscopic studies revealed the lumen of the aorta to be occupied by a large antemortem thrombus with early canalization and basal organization. There was an infiltration of lymphocytes and histiocytes with edema between the adventitia and media. The large arterial branches were similarly involved. Other gross pathological changes were corroborated by extensive microscopic studies. The final diagnosis was inactive rheumatic heart disease with mitral stenosis and insufficiency, with embolization to the abdominal aorta, and thrombosis of the mesenteric, iliac, splenic and renal arteries.

Comment. The age, cardiac history, rheumatic heart disease with fibrillation, normal aorta, multiple embolization for two years (brain, kidneys, spleen, superior mesenteric artery and extremities) were completely in harmony with the diagnosis of an aortic occlusion due to embolization. This interesting case was carefully followed for two years. It was remarkable to note that although the acute symptoms dated back 11 days before death and produced various clinical pictures of acute cholecystitis, acute appendicitis, peptic ulcer and mesenteric thrombosis, the extremities remained uninvolved and findings were localized to the abdomen only. Hence, although the diagnosis was not made, mesenteric thrombosis was correctly suggested. Terminally, the thrombotic process progressed rapidly on the embolic nidus.

Case 2. E. M., white, married, Puerto Rican female, aged 34, was admitted with sudden onset of excruciating pains in both legs with inability to walk, numbness and coldness of both feet. After an hour she developed sharp knife-like pains in both calves and was unable to move either leg. They felt cold and numb and the pain became dull and aching. The following day she requested hospital treatment. Her past history revealed attacks of dizziness, dyspnea, palpitation and edema. She had had intermittent attacks of joint pains involving chiefly the right leg and knee over a 10 year period.

Physical examination revealed an enlarged heart with harsh presystolic and systolic apical murmurs and a systolic apical thrill. Blood pressure was 150 mm. Hg systolic and 70 mm. diastolic. There was no enlargement of the liver or spleen.

Aortic pulsations were felt to a level just below the umbilicus. No pulsations were palpated in the femoral, iliac, popliteal and dorsalis pedis arteries. The right leg was more involved than the left and was cold, clammy, blue and dry. Although the sensation of touch was decreased, pressure and pain were exaggerated. The calves were edematous, swollen and firm. A diagnosis of enlarged heart due to rheumatic heart disease, mitral stenosis and insufficiency, ventricular extrasystoles, class II A, was made. In addition, a diagnosis was made of a rider's embolus possibly due to a subacute bacterial endocarditis. The condition progressed steadily until bilateral mid-thigh lines of demarcation formed. It was of interest to note the clear outlines of the capillaries on the plantar surfaces with mummification by dry gangrene. Treatment consisted of large doses of papaverine, dry heat and an oscillating bed, since surgical intervention was not advisable. The temperature ranged between 99 and 103° F. The patient gradually became worse and finally died 17 days later.

Laboratory Studies. The electrocardiograph showed auricular hypertrophy, right axis deviation and myocardial damage. A bedside roentgenogram revealed an enlargement to the left and enlargement of the left auricle due to rheumatic heart disease. Two blood Wassermann reactions were negative. Three blood cultures taken for *Streptococcus viridans* were negative. The leukocyte count was 10,000 with 94 per cent polynuclears.

Autopsy revealed both lower extremities to be reddish black, swollen and gangrenous with many vesicles containing clear fluid. The heart weighed 360 grams and presented rheumatic endocarditis with stenosis of the mitral, aortic and tricuspid valves. Pearly-gray excrescences were present over the thickened valve edges. Many small and large round and odd shaped vegetations were found over the auricular surfaces. One of these vegetations occluded the ostium of a Thebesian vessel. The aorta and large branches appeared thin-walled and elastic throughout. At the level of the fifth lumbar vertebra, the lumen of the aorta was occluded by a soft, grayish-red thrombus that was firmly attached to the intima and extended beyond the bifurcation of the femoral arteries. A branch of the pulmonary artery supplying the right middle lobe was occluded by a soft, adherent antemortem thrombus with pulmonary infarctions. On microscopy, the intima of the aorta consisted of many layers of hyalinized connective tissue. The media was replaced by a considerable amount of dense connective tissue. The adventitia and vasa vasorum were not unusual. In the sections exhibiting the thrombus there were masses of red blood cells, polynuclears and proliferating fibroblasts enmeshed in fibrin. Sections of the auricle showed similar areas of attached thrombi with infiltrating fibroblasts and small mononuclear cells. The adjacent muscle cells were necrotic.

The final diagnosis was rheumatic endocarditis with stenosis of the mitral, aortic and tricuspid valves with marked hypertrophy and dilatation of the heart. Secondary embolization from the heart to the abdominal aorta with succeeding thrombus proliferation resulted.

Comment. Embolization from the left auricle was the cause of aortic obstruction in this case. The age, rheumatic history, cardiac findings, acute onset of pulmonary infarction and elastic aorta and branches were all in its favor. Embolectomy was the treatment of choice but the patient sought relief two days after the onset. The immediate use of a constantly oscillating bed, papaverine and dry heat undoubtedly prolonged her life for two weeks despite the severity of the occlusive process.

Case 3. J. H. (case of Dr. B. A. Fedde), white male, janitor, aged 50, was admitted with pain in the epigastrium and the lower right quadrant. He had had malaria 36 years previously and had been operated on for chronic appendicitis one

year earlier. Thirty years previously he had been crushed by a car in a coal mine, the maximum impact being at the umbilicus. He had had three attacks of gonorrhea and drank heavily until two years prior to admission. He was unable to walk more than three blocks without getting severe cramps in both legs requiring rest for several minutes before continuing. His feet were generally cold.

Examination revealed a poorly nourished male. The heart apex was in the sixth interspace in the midclavicular line. No murmurs or irregularities were heard. Blood pressure was 130 mm. Hg systolic and 90 mm. diastolic. There was a hernia at the site of the previous operation as well as a right femoral hernia. The brachial artery was tortuous and sclerotic and the dorsalis pedis and posterior tibial artery pulsations could not be palpated. Because of abdominal and loin pain, a right ureteral calculus was considered. Pyelography revealed a mobile right kidney with slight hydronephrosis due to uretero-pelvic kinking. Right ureterolysis and nephropexy were performed. The immediate postoperative condition was good. However, the following day he complained of pain in both legs followed shortly by a mottled, purple discoloration. Although both legs were fairly warm at first, pulsations were not felt in the femoral, popliteal or tibial arteries bilaterally. The reflexes were lost and the extremities became cold in an hour and a half, more markedly on the right. A diagnosis was made of a postoperative saddle thrombus. Surgery was deemed futile and the patient died the same day. The temperature course was normal throughout.

Laboratory. Roentgenographic studies revealed a normal gall-bladder and gastrointestinal tract. Calcification of the iliac vessels was noted. There was no free acid and 23 to 45 points of total acidity on gastric analysis. Blood chemical tests, Wassermann reaction, three urinalyses and urine culture were negative.

Autopsy revealed the recent loin incision and nephropexy which were uninfected. The heart weighed 360 grams. The left ventricle measured 1.4 cm. in thickness. The valves and endocardium were free of vegetations or thrombi. The intima of the aortic arch presented numerous non-ulcerating atheromatous calcified plaques. A large thrombus was found completely occluding the aorta from the renal arteries to its bifurcation. The thrombus was firm, friable, dark red and firmly adherent to the intimal surface. Just below the upper end of the thrombus was a ring of calcified hard atheromatous degeneration which was ulcerated but there was no point of rupture of the aorta. The thrombus extended into the iliac arteries and their branches. The right iliac vessel was dark blue, having undergone a marked degree of atheromatous degeneration. There was no evidence of renal infarction and the right renal artery was free of sclerosis. On the left side, the artery consisted of a section of thin, fibrous tissue interposed between two stumps of normal artery. There was an aberrant vessel arising 0.5 cm. above the site of the normal renal artery which entered the lower pole of the left kidney after crossing the normal artery. This vessel was slightly narrowed at the point of crossing but contained no thrombus.

Comment. An evaluation of the factors involved in this case is somewhat complex. Undoubtedly the primary factor concerned with the production of the aortic occlusion was the ulcerated ring of calcified atheromatous degeneration near the renal arteries, most marked just below the upper end of the thrombus. The marked calcification of other blood vessels strengthens this belief. What additional influence, if any, the aberrant renal artery played is difficult to ascertain since there was no thrombosis or sclerosis of the renal vessels beyond the occlusion at the mouths of these vessels. Probably this congenital defect played a very small rôle. Although trauma is an accepted cause for thrombosis, certainly the crushing impact at the umbilicus could not have been expected to exert any influence after 30

years. It is conceivable that traction at the time of nephropexy, however, may have contributed some measure of trauma at the site of the ulcerated ring. The precipitating factor producing a thrombus at this site was the increase in platelets and fibrinogen which follow any operation. In addition, there was an initial drop in blood pressure during operation with a slowed blood stream which aided clot formation. Hemoconcentration also occurred from loss of fluids and blood, as well as vomiting, diuresis and acidosis. The importance of this factor arises from the physical fact that the velocity of a fluid in a tube is inversely proportional to its viscosity and directly proportional to the driving pressure to which it is subjected. The fact that thrombosis may occur in different blood systems of the body (e.g., pulmonary artery and portal vein as in case E. M.) also speaks strongly for the influence of these factors. This has been noted elsewhere.[1]

Case 4. R. H. (case of Dr. G. A. Merrill), white housewife, aged 62, was admitted with a stroke of six hours' duration. She had had a heart attack of an unknown type six months previously, and had been given digitalis until one month before admission.

Examination revealed a well developed female with a complete right hemiplegia and aphasia. The heart was slightly enlarged and rhythm was regular. Blood pressure was 160 mm. Hg systolic and 110 mm. diastolic. There were a few basal râles. The diagnosis was arteriosclerotic heart disease with thrombosis of the left middle cerebral artery. Except for urinary incontinence she progressed fairly satisfactorily. Eleven months later she suddenly become comatose with left hemiplegia and died two days later.

Laboratory studies included an electrocardiogram which presented left axis deviation and severe myocardial damage. Blood chemical tests and Wassermann reaction were normal. The temperature was normal throughout.

Autopsy examination of the brain revealed a fresh thrombus of the right middle cerebral artery. The heart weighed 425 grams and revealed moderate coronary sclerosis and myocardial fibrosis. The aorta presented a marked atherosclerosis with a saddle thrombus at the bifurcation of the aorta extending into both common iliac and right internal iliac arteries with complete occlusion. The entire length of the thrombus was 10 cm. There were large ulcerated plaques at the bifurcation of the aorta. In addition, there were an acute hemorrhagic cystitis, gastric polyp and generalized arteriosclerosis.

Comment. Undoubtedly, the age, generalized arteriosclerosis, regular sinus rhythm without mural thrombi, old and recent thrombotic occlusions of the cerebral vessels, marked atherosclerosis of the aorta with large ulcerated plaques at the bifurcation are all in favor of a thrombo-arteriosclerotic process. The unusual feature of this case is that although she was acutely ill for two days she presented no symptoms or signs of aortic thrombosis. The conclusion one may safely draw is that the extensive thrombosis developed rapidly just prior to death.

Case 5. E. B., white unemployed male, aged 80, was admitted with cellulitis of the lower extremities and dyspnea. He had been troubled with asthmatic bronchitis and expectoration for a half year but was in excellent health previously.

Examination revealed occasional coarse moist râles, especially at the bases, and rhonchi throughout. The heart sounds were regular but of poor quality and no mur-

murs were present. Blood pressure was 140 mm. systolic and 70 mm. diastolic. A diagnosis of bronchiectasis with secondary emphysema was made. He became increasingly weaker with terminal fibrillation and died one and a half years after admission.

Laboratory examinations included an electrocardiographic study presenting evidence of myocardial fibrosis. Roentgen-ray revealed no pulmonary disease. Blood Wassermann reaction was negative. The temperature never was above 100.5° F.

Autopsy revealed bronchiectasis of both lower lobes with terminal bronchopneumonia. The heart weighed 280 grams and showed evidence of myocardial fibrosis. The arch and ascending aorta were moderately dilated with many sclerotic plaques. The thoracic and abdominal aorta had many small sclerosed plaques some of which were calcified and ulcerated. There was a large thrombus occluding the abdominal aorta for a distance of 5 cm. above the bifurcation. On section, the thrombus contained a large area filled with soft red necrotic material. The thrombus did not extend into the left common iliac artery, but in the right common iliac artery there was a small red-gray thrombus which partially occluded the lumen. The external appearance of the body was negative. The final diagnosis was atherosclerosis with ulceration and thrombosis of the abdominal aorta and the right common iliac artery.

Comment. This occlusion was due to thrombo-arteriosclerosis of the aorta. As in the preceding case, there was no subjective or objective evidence to suggest thrombosis of the abdominal aorta even just prior to death.

Case 6. A. D., white female, aged 38, previously in fair health, suddenly lost consciousness the night before admission. During childhood she suffered from "growing pains" and recently developed shortness of breath. Two years before she was told she had heart disease.

Examination revealed an obese female with dyspnea and cyanosis. The heart was slightly enlarged to the left with a double apical murmur and auricular fibrillation. Blood pressure was 120 mm. Hg systolic and 80 mm. diastolic. There was a complete left hemiplegia which a neurological consultant thought was caused by embolism of the lenticulo-striate artery due to rheumatic heart disease with auricular fibrillation. She became incontinent and emotionally unstable. Eight days later she suddenly developed signs of pulmonary infarction in the left upper lobe which subsided in two days. Three days later she suddenly developed marked blueness and paralysis of both legs, and pulsations in the dorsalis pedis and other leg arteries were not palpable. She died six hours later. Treatment consisted of digitalization and supportive management.

Comment. This case was undoubtedly one of embolism. The age, rheumatic history, auricular fibrillation with cerebral and pulmonary embolism are definite evidences of further embolism to the bifurcation of the aorta.

Case 7. G. S. (case of Dr. J. Hamilton Crawford), a white unemployed male, aged 65, was admitted in shock with a history of sudden collapse and vomiting with severe pains and paralysis of both legs. The pains began in the inguinal regions, shot down into the legs and were also present in the lower back. Three months before he collapsed with sudden pain in the left leg while walking. He had been getting intravenous injections for leg pains twice weekly at a hospital clinic.

Examination revealed a state of severe shock. There was exquisite tenderness over both lower quadrants and the hypogastrium. The extremities were blue, cold, and mottled and the femoral, popliteal and dorsalis pedis artery pulsations were not present. The reflexes were absent and there was a flaccid paralysis of the legs. Pain sensation was absent from the first to the fifth lumbar segments. Vibration sensation

was lost below the fourth lumbar segment and iliac crests. A diagnosis of saddle thrombus was made. Because of profound shock operation was deemed inadvisable. Despite papaverine and nitroglycerine intravenously every three hours, glucose by hypodermoclysis and other supportive measures, the patient died 18 hours after the onset. The admission temperature of 98° F. mounted to 104° terminally.

Autopsy revealed a heart that weighed 300 grams. The valves and heart cavities were negative. The aorta showed evidence of ulcerating atheromatous lesions in the thoracic portion. The lower portion of the abdominal aorta was completely occluded by a mass of light red soft thrombus markedly adherent to the wall, 7.5 cm. proximal to the bifurcation. The immediate wall was dark blue and calcified. Proximally, there was a characteristic long "currant jelly" clot. Both common iliac, hypogastric and external iliac arteries were markedly sclerotic and filled with the same material. On microscopy, there were atheromatous plaques with ulceration and adherent thrombi. Sections of the large arteries showed marked atherosclerosis with medial necrosis and occasional areas of slight round cell and histiocytic infiltration with endarteritis of several of the vasa vasorum. Final diagnosis was advanced atherosclerotic calcification with ulceration and complete thrombotic occlusion of the lower abdominal aorta, common iliac, external iliac and hypogastric arteries.

Comment. This case is obviously one of thrombo-arteriosclerosis of the aorta and large vessels with typical symptoms and findings. The process started three months previously with thrombosis of the left femoral artery with subsequent proximal occlusion to the bifurcation and then down the opposite common iliac and major branches. Operation was impossible because of profound shock.

Case 8. A. W., white female, aged 84, was admitted with spells of vomiting of six hours' duration. She was found on the floor screaming and vomiting foul brown material. Previous history was negative except for slight, old right facial paralysis.

Examination revealed negative cardiac findings. Blood pressure was 214 mm. Hg systolic and 138 mm. diastolic. There was abdominal tenderness with a suggestive mass in the left lower quadrant. Pelvic and rectal examinations were negative. The bladder was distended requiring catheterization. Diagnoses of carcinoma of the bladder or of mesenteric thrombosis were considered. She improved gradually and was to be discharged 25 days later when she developed a bilateral parotitis. Two days later the temperature suddenly rose to 104° F. and the patient went into coma and died. Terminally, she presented signs of a bilateral diffuse bronchopneumonia. Treatment was symptomatic.

Laboratory examinations included an electrocardiogram which showed left axis deviation and coronary sclerosis with marked myocardial degeneration. The Wassermann reaction was negative. The blood urea, creatinine and sugar were 98, 1.8 and 114 mg. per 100 c.c., respectively. The leukocytes were 13,250 per cu. mm. with 78 per cent polynuclears. The urine contained albumin (three plus) with occasional red and white cells and hyaline and granular casts.

Autopsy. The heart weighed 375 grams, the left ventricle was 2.5 cm. thick, but the valves and endocardium were negative. Just above the aortic valve there was a denuded area 2 cm. in diameter which contained soft debris and calcific flakes. Just above its bifurcation the aorta was distended by a fusiform swelling which on section was found to contain a thrombus of recent origin. Its posterior surface presented atheromatous plaques and ulcerations. The clot completely occluded the aortic lumen. Microscopy revealed typical atheromatous degeneration with recently superimposed thrombus formation. In addition, there were nephrosclerosis, generalized arteriosclerosis and bronchopneumonia. The extremities appeared normal in every respect.

Comment. This occlusion was caused by thrombosis superimposed on an arteriosclerotic aneurysm of the abdominal aorta. Although the patient presented no subjective or objective findings other than a suggestive mass in the left lower quadrant, there was a gradual thrombotic process which became rapidly occlusive just prior to death.

Case 9. H. T. (case of Dr. C. H. Greene), white female houseworker, aged 39, was admitted with a history of pains about the girdle and both lower extremities and weakness of the legs. She was irrational and confused.

Examination revealed flaccid paralysis of both lower extremities and bilateral foot drop. All reflexes and sensations were absent in the legs. There was muscle tenderness and pain on passive motion of the legs. The right leg was very cold below the knee, and the left leg was cold below the midleg. Later this extended irregularly to about the mid-thigh. The dorsalis pedis artery pulsations were not palpated. Following a neurosurgical consultation by Dr. J. Browder, three days later, it was thought that an occlusion of the abdominal aorta existed at the iliac bifurcation. The patient died without operation six days later because of the bilateral extent of the gangrene.

Laboratory studies revealed normal spinal fluid, blood chemical tests and Wassermann reactions. The white cell count rose from 38,900 to 66,300 (with 81 per cent polynuclear neutrophiles) in three days. The temperature was normal throughout. Roentgenographic examination suggested the presence of a left iliopsoas mass.

Autopsy. The heart weighed 520 grams and contained no thrombi or vegetations. Situated at the bifurcation of the aorta was a "saddle-back" thrombus extending 1¼ inches upward into the aorta, 2 inches into the right common iliac artery and 1 inch into the left common iliac artery, both of which were completely occluded. The thrombus was well organized, gray-white and very adherent to the intima. There was a bilateral abscess involving the lower fourth of the psoas muscles. A small tumor overlying the fifth lumbar vertebra proved to be a reticulum cell sarcoma which invaded this vertebra with secondary psoas abscesses. Other sections of the aorta presented myxomatous degeneration of the intima and media with organizing adherent thrombus. Significantly, the periaortic tissues exhibited septic thromboses of the capillaries.

Comment. The sequence of events in this case began with a small reticulum cell sarcoma which invaded the fifth lumbar vertebra. Microscopic sections proved that the aorta itself had not been invaded by the neoplasm. However, secondary infection with the formation of bilateral psoas abscesses produced both infection and pressure upon the aorta with resultant aortic thrombosis. The septic thromboses of capillaries in the periaortic tissues tend to bear out this observation. The age, normal valves, heart cavities and aorta, and negative history rule out an embolic or thrombo-arteriosclerotic origin.

Case 10. H. M., white female, aged 49, was admitted with a complaint of pains in both legs of five hours' duration. She was awakened by sudden stabbing, burning pains from the hips to the toes of both legs. They became blue, cold, then gray-white, with loss of all sensation except the excruciating pains. She had had auricular fibrillation five years previously and had been taking digitalis irregularly because of nausea. She had had scarlet fever at the age of eight but gave no other history of cardiorenal disease.

Examination revealed cardiac enlargement to the left with an irregular rate of 110 per minute. There were apical systolic and aortic diastolic murmurs and the sounds were of fair quality. The blood pressure was 168 mm. systolic and 108 mm. diastolic. Both legs were cold and mottled. The right leg was slightly less involved. All sensations were absent. No popliteal or dorsalis pedis artery pulsations were present in either extremity. A diagnosis was made of rider's embolus to the aortic bifurcation due to rheumatic heart disease with mitral insufficiency and stenosis, auricular fibrillation, class IV D. The patient was given large doses of papaverine, whiskey, aminophyllin and digitalis. She was also placed in a Sander's oscillation bed for six weeks constantly and was then able to get up and walk about, gradually and with assistance. This treatment was supplemented by a continuous temperature of 90° F. maintained by thermostatic-controlled light. Later she was given daily treatments with indirect ultra-short wave therapy to the lower back.

She began to show considerable improvement on the second day, with decreased intensity of pain and increased warmth. The legs became blue-red and sensation returned. There were no trophic changes. No pulsations were yet palpated in either popliteal or dorsalis pedis artery and in the left femoral artery. Four days after the onset, oscillometric readings showed none to be present in the left foot, leg and popliteal arteries. There was no dorsalis pedis pulsation on the right with a fibrillating swing of 4 to 8 in the tibial and popliteal arteries. The skin temperature showed a marked drop in the left limb. One month later there was noted marked blanching of the left foot with continued rubor of the right foot. On dependency, there was a lag with continued pallor for over 45 seconds, followed by no increase in pink color. The oscillometer showed no pulsations three days later. Skin temperature readings before and after the Landis-Gibbon test (temperature water 120° F. for 20 minutes) showed organic changes by the drop in skin temperature readings. Three weeks later these skin temperature readings presented a marked drop ranging from one to two degrees fall indicating a marked vasospasm. The oscillometric readings after the Landis-Gibbon test showed the same low or absent pulsations in the feet and left leg with some rise in the right thigh. One month later, examination revealed marked scaling of the right foot and toes. On elevation there was mild plantar ischemia on the left and pinkness on the right. On dependency, there was dusky cyanosis on the left and pallor on the right. The dorsalis pedis and posterior tibial pulsations on the right were present. The left dorsalis pedis was very faint and the left posterior tibial and femoral arteries were faint. She was able to walk alone without discomfort. Oscillometric readings showed marked improvement in pulsations indicating a canalization of the occluded vessels. The histamine test showed a delay in wheal formation up to five minutes on the left, but a fair reduction after 10 minutes indicating good surface circulation. In spite of the apparent subjective improvement there was a consistent fall in skin temperature following the Landis-Gibbon test which brought up the possibility of a marked spastic element. She was discharged two months after admission, greatly improved, with a final diagnosis of rheumatic heart disease with mitral insufficiency and stenosis, auricular fibrillation and embolism to the bifurcation of the aorta.

Further laboratory studies revealed normal Wassermann reaction, urinalysis and blood counts. The temperature course was normal throughout.

Comment. This case is remarkable in that recovery and recanalization occurred from an embolic process to the aortic bifurcation with intensive medical treatment that did not include surgery or heparin therapy. Measures that were vigorously applied included immediate use of large doses of papaverine, whiskey and aminophyllin, as well as such physical measures as the oscillation bed, controlled dry heat and remote ultra-short wave therapy.

The diagnosis of embolism to the aortic bifurcation due to auricular fibrillation is unquestioned because of the cardiac history, sudden bilateral leg involvement with pains from the hips down and absent pulsations in both legs noted by oscillometer recordings and Landis-Gibbon test. The gradual improvement was carefully noted with oscillometer and skin temperature recordings. At the present time the circulation of the extremities remains adequate.

Case 11. L. B. (case of Dr. D. M. McCarthy), white Italian male, aged 52, handy man, was admitted in an unconscious state with a history of a left sided "stroke" one year previously and again five months previously, causing him to be bedridden. There were no headaches or sphincter disturbances.

Examination revealed a left hemiplegia due to right middle cerebral artery thrombosis. Because of loss of vision in his right eye fundoscopy was done which revealed primary optic atrophy due to central retinal artery thrombosis. Blood pressure was 145 mm. systolic and 90 mm. diastolic. Two weeks later bronchopneumonia developed at both bases which cleared up with sulfapyridine therapy in four days. One week after this, it was noted that the patient suddenly seemed restless and complained of abdominal pains. Both legs developed coldness and a blotchy appearance and all arterial pulsations were lost in the legs. A diagnosis of possible saddle thrombosis was made. The following day both extremities continued to remain cold, cyanotic and pulseless. Before a surgical consultation could be undertaken the patient died suddenly on the third day. There was a temperature rise of two degrees terminally.

Laboratory Findings. Blood and spinal Wassermann reactions, colloidal gold test, blood and spinal fluid chemical findings and urinalysis were entirely normal.

Autopsy. The left leg was somewhat more swollen than the right. The heart weighed 350 grams. The valves were all competent. There were multiple infarctions of the kidneys. An old cerebral thrombosis was found. At the arch of the aorta about 4 cm. above the aortic cusps was a firm, raised, yellowish-pink vegetation firmly attached to an atheromatous plaque of the aorta and measuring 5 cm. in diameter. Elsewhere, the aorta was smooth and glistening except at the bifurcation, where there was a firm antemortem thrombus, 6 cm. long, closely adherent and extending about 4 cm. into both common iliac arteries. Microscopy revealed marked atherosclerotic degeneration. The intima was covered by a thin layer of fibrin and a recent antemortem thrombus which showed early basal organization. The media presented marked vascularization of the outer and middle thirds, and the adventitia showed marked fibrosis, vascularization and round cell infiltration.

Comment. This is a case of thrombo-arteriosclerosis of the aorta. Two areas of arteriosclerosis with superimposed vegetations were found in the ascending aorta and at the bifurcation. The cerebral, retinal and renal lesions were probably due to embolization from the former area of thrombo-arteriosclerosis. The saddle thrombus and the marked underlying atherosclerosis and similarity to the upper aortic process would rather speak for an arteriosclerosis with rapid thrombotic occlusion at this site.

Case 12. C. M., white female, aged 41, was admitted with complaints of sudden onset of cold, paleness and pain in both legs of 36 hours' duration. She also had abdominal and back pains and bloody urine. She gave a history of rheumatic heart disease for six years. She had edema and dyspnea for the past few years but she was not taking digitalis.

TABLE I

Case	Patient	Age	Sex	Symptoms			Findings		Laboratory	
				Past History	Location of Pain in Extremities	Other Symptoms	Findings Extremities	Other Findings	Positive Laboratory Findings	Wass
1	F.O.	32	F	1) Mitral stenosis—at 21 yrs. 2) Rt. hemiplegia—6 mos. ago 3) Pulmonary infarction—2 wks. ago 4) Pulmonary edema—2 yrs. ago 5) Pain in L.U.Q. (splenic infarct)—2 yrs. ago 6) Embolus left leg—2 yrs. ago	None	R.U.Q. pain, vomiting	None	R.U.Q. tenderness B.P. 170/95	X-ray: prominent pulmonic conus EKG: Neg.	—
2	E.M.	34	F	Rheumatic joints—10 yrs.	Sudden onset excruciating pains both legs, paraplegia		Both legs cold, clammy, blue, absent pulsations of aorta below umbilicus, touch absent, pain and pressure increased	B.P. 150/70	EKG: right axis deviation X-ray: left side enlargement	—
3	J.H.	50	M	1) Arteriosclerosis extremities 2) Nephroptosis with nephrolithiasis	Pain both legs		Cold, reflexes and all pulsations absent	B.P. 130/90	X-ray: calcification iliac vessels	—
4	R.J.	62	F	1) Heart attack—6 mos. ago 2) Stroke—6 hrs. also 11 mos. ago	None		None	Sudden coma B.P. 160/110	EKG: Severe myocardial damage	—
5	E.B.	80	M	Bronchiectasis	None	Weakness cough	None	B.P. 140/70	EKG: myocardial damage	—
6	A.D.	38	F	Rheumatic history since childhood	Blueness and paralysis of both extremities		Absent pulsations both legs with marked blueness and absent reflexes	B.P. 120/80		—
7	G.S.	65	M	Treatment for arteriosclerosis of leg vessels—3 mos.	Severe pains in inguinal regions radiating down legs and lower back		Blue, cold, mottled, paralysis with absent reflexes and sensations. Tenderness over hypogastrium and both lower quadrants	Shock		
8	A.W.	84	F	Old right facial paralysis	None	Fecal vomiting	None	Suggestive mass in L.L.Q. B.P. 214/138	EKG: marked myocardial degeneration, left axis deviation. Blood urea 98 mg., leukocytes 13,200	—
9	H.T.	39	F	None	Pains about girdle and lower extremities with weakness legs		Flaccid paralysis both legs with absent sensation and reflexes. Gangrene both legs		Leukocytes 66,300	—
10	H.M.	49	F	1) Scarlet fever at 8 yrs. 2) Auricular fibrillation 5 yrs. ago	Sudden burning and stabbing pains from both hips to toes		Cold, mottled blue legs with no sensation or pulsations	B.P. 168/108	Oscillometer: no pulsations. Landis-Gibbon test: organic arterial occlusion	—
11	L.B.	52	M	Left hemiplegia—5 mos. and 1 yr. ago	None	Abdominal pain	Cold, cyanotic extremities without pulsations	Blindness right eye B.P. 145/90		—
12	C.M.	41	F	Rheumatic heart disease—6 yrs.	Cold, paleness and pain both legs	Bloody urine, abdominal and back pains	Absent pulsations, superficial gangrene, cold and mottling	Renal tenderness B.P. 110/60	Oscillometer: no pulsations of legs. Urine: albumin, casts, red and white cells	—
13	L.F.	61	F	1) Rheumatic fever at 15 and 25 yrs. 2) Left hemiplegia—2 yrs. ago 3) Diabetes—4 yrs.	Sudden sharp pain in right thigh	Severe pain rt. lumbar, dizziness, profuse perspiration	Coldness up to umbilicus. Pulsations and sensation. Paraplegia absent	Rt. lumbar tenderness. Shock B.P. 176/70	Urine: albumin, sugar, red and white cells. X-ray: enlarged left ventricle and aortic arch with sclerosis EKG: auricular fibrillation after heart block	—
14	R.V.	47	F	1) Decompensation and rheumatic heart disease—for many years 2) Pulmonary infarction—1 month ago	Sudden onset sharp excruciating pain. Paralysis right leg		Complete absence pulsations both legs, marked cyanosis from hip to knee right leg with beginning gangrene below. Absent sensation rt. leg	B.P. 150/80	Urine: albumin, pus clumps Leukocytes: 14,000, 92% polynuclears	

TABLE I—*Continued*

Clinical Diagnosis	Other Diagnosis Considered	Pathology								Etiology	Occlusion of Other Vessels	Clinical Diag. Corroborated	Duration of Acute Condition	Treatment
		Heart Weight	Aortic Bifurc.	Common Iliac		Ext. Iliac		Int. Iliac						
				R	L	R	L	R	L					
Rheumatic heart disease, auricular fibrillation, multiple emboli	Mesenteric thrombosis, peptic ulcer, acute cholecystitis, acute appendicitis	210	+	+	+					Embolus	1) Renal 2) Splenic 3) Sup. and inf. mesenteric 4) Left middle cerebral	No	11 days	Symptomatic digitalis
Rheumatic heart disease with embolization	None	360	+ Up to renal arteries	+	+	+	+	+	+	Embolus	Pulmonary artery	Yes	17 days	Oscillation bed, papaverine, dry heat
Post-operative saddle thrombus	None	360	+ Up to renal arteries	+	+	+	+	+	+	Thrombo-arteriosclerosis + post-operative thrombocythemia		Yes	1 day	Papaverine
Arteriosclerotic heart disease, left hemiplegia	None	425	+	+	+			+		Thrombo-arteriosclerosis	Both middle cerebral arteries	No	2 days	Symptomatic digitalis
Bronchiectasis	None	280	+	+						Thrombo-arteriosclerosis		No	?	Symptomatic
Rheumatic heart disease with embolization, auricular fibrillation	None	—		No autopsy						Embolus	1) Lenticulostriate artery 2) Pulmonary artery	No autopsy	6 hours	Papaverine, nitroglycerine, glucose clyses
Saddle thrombus	None	300	+	+	+	+	+	+	+	Thrombo-arteriosclerosis		Yes	18 hours	Symptomatic
Mesenteric thrombosis or carcinoma of bladder	Same	375	+							Mural thrombus + abdominal aneurysm		No	4 weeks	Supportive
Saddle thrombus	Tabes, cord tumor	520	+	+	+					Infection		Yes	6 days	Supportive
Rheumatic heart disease with auricular fibrillation and rider's embolus	None	—		Recovery by recanalization						Embolus		Recovered	2 mos.	Oscillation bed constantly continuous dry heat at 90°, papaverine, aminophyllin, whiskey, digitalis. Indirect ultra-short wave therapy
Saddle thrombus	Pelvic thrombophlebitis	350	+	+	+					Thrombo-arteriosclerosis	1) Central retinal artery—right 2) Middle cerebral artery 3) Renal arteries	Yes	2 days	Symptomatic
Rheumatic heart disease with auricular fibrillation and embolization	None	—		No autopsy						Embolus	Renal artery	No autopsy	5 days	Digitalis, dry heat, morphine
Rheumatic heart disease with auricular fibrillation and multiple emboli. Diabetes mellitus	Renal infection, later, rider's embolus	490	+	+	+	+	+	+	+	Embolus	Renal artery	Yes	16 days	Theophyllin, morphine
Rheumatic heart disease with auricular fibrillation and saddle embolus	None	—		No autopsy						Embolus	Pulmonary artery	No autopsy	4 weeks	Papaverine, cold packs

Examination revealed a heart slightly enlarged to the left. At the apex there was a presystolic thrill and rumble followed by a diastolic murmur and there was auricular fibrillation. Blood pressure was 110 mm. Hg systolic and 60 mm. diastolic. The liver was two fingers' breadth below the costal margin and the spleen was just palpable. There was marked renal tenderness. The left leg from the knee down was warm and swollen, with superficial gangrene of the medial and lateral aspects. The femoral, popliteal and dorsalis pedis arterial pulsations bilaterally were not palpated or heard. There was some precordial pain and dyspnea. Diagnosis made by the medical staff and surgical consultants was mitral insufficiency and stenosis due to rheumatic heart disease with auricular fibrillation. Embolization to the kidneys and aortic bifurcation with early gangrene of both legs were secondary, but embolectomy was deemed impossible because of the age of the condition. She was given morphine, dry heat and digitalis and died four days after admission.

Laboratory examinations included oscillometer recordings on admission, which revealed no thigh pulsations as compared with normal responses in the arm. Two blood cultures were negative. The blood urea and creatinine were 80 and 2.1 mg. per 100 c.c., respectively. Urinalysis repeatedly showed the presence of marked albuminuria, granular casts and many red and white blood cells. The temperature ranged between 100 and 104° F. Autopsy was refused.

Comment. The age, history of rheumatic heart disease, cardiac findings, congestion with auricular fibrillation, renal embolism, negative oscillometer readings and bilateral involvement of the extremities are indicative of further embolization at the bifurcation of the aorta.

Case 13. L. F., white female houseworker, aged 61, was admitted with severe pain in right lumbar region, dizziness and profuse perspiration for 24 hours. She had had diabetes for four years which was controlled by a 1500 calorie diet. She had had attacks of rheumatic fever at 15 and 25 years of age and was thereafter short of breath on exertion or lying down. She suffered a left "stroke" two years before and 10 days before developed a slight paralysis again.

Examination revealed the heart to be enlarged to the left with a loud blowing systolic apical murmur. The heart rate was 48 per minute and the blood pressure was 176 mm. Hg systolic and 70 mm. diastolic. There was pain and tenderness over the right iliac crest. In view of the finding of marked albuminuria and white and red cell clumps in the urine, a diagnosis of renal infection was considered. Two weeks after admission, the patient was seized with a sudden agonizing pain in the back of the right thigh, followed by coldness, blueness, paralysis and loss of sensation of both lower extremities. Auricular fibrillation and pulmonary edema occurred. No arterial pulsations were palpable. Dr. J. H. Crawford made a diagnosis of rider's thrombus preceded by renal infarction. The coldness extended to an area below the umbilicus corresponding to the tenth dorsal nerve root. In view of the profound shock and fibrillation, embolectomy was deemed impossible. Despite supportive therapy, aminophyllin and morphine the patient died the following day.

Laboratory findings revealed a negative Wassermann reaction and blood sugars ranging from 444 down to 286 mg. per 100 c.c. Urine sugars were two to three plus, after 30 units regular insulin daily. Blood urea and creatinine were normal. Roentgenographic examination revealed moderate enlargement of the left ventricle with sclerosis and enlargement of the aortic arch. Electrocardiographic tracing on admission exhibited auricular fibrillation, complete heart block with idioventricular rhythm and myocardial damage. This changed to slow auricular fibrillation ten days later.

Autopsy revealed marked obesity and generalized arteriosclerosis. The heart weighed 490 grams and contained no thrombi. The mitral leaflets were markedly thickened and retracted and the chordae tendineae were short and thickened. There were no vegetations or verrucae. The right kidney presented a large infarction. The aortic intima was smooth in the thorax, but below the diaphragm there were occasional yellow atheromatous areas with early calcification. Just above the bifurcation and extending bilaterally into the common iliac, external iliac and hypogastric arteries was a large completely occlusive antemortem thrombus which was firm, friable and clearly adherent to the wall. The other medium sized vessels were thin-walled and elastic. Microscopy revealed an antemortem thrombus in early stages of organization with slight calcification in the media. Final diagnosis was saddle thrombus, infarction of right kidney, chronic passive congestion of all organs and healed rheumatic mitral valvulitis with stenosis.

Comment. Despite the advanced age and early calcification of the aorta, this case is obviously of embolic origin. This is borne out by the rheumatic history, cerebral and renal emboli, cardiac findings with auricular fibrillation and bilateral involvement of the extremities. The additional influence of a markedly slowed blood stream as evidenced by the complete heart block and subsequent slow auricular fibrillation and terminal pulmonary edema allowed for a more rapid increase in thrombus formation. Embolectomy was impossible because of profound shock and pulmonary edema.

Case 14. R. V., white housewife, aged 47, was admitted with a history of sudden onset of excruciating pain in her right leg for two hours with absent sensation and inability to move the leg. Past history revealed that she had rheumatic heart disease with attacks of decompensation for many years. One month before she developed a pulmonary infarction.

Examination revealed moderate cardiac enlargement with a double murmur at the apex and auricular fibrillation. Blood pressure was 150 mm. systolic and 80 mm. diastolic. There were basal râles. There was complete absence of pulsations in both legs. Marked cyanosis of the right leg from the hip to the knee was present with complete blanching. Sensation was absent below the knee and the patient was unable to move her leg. A diagnosis of rheumatic heart disease with auricular fibrillation and embolization to the bifurcation of the aorta was made. The patient was given papaverine and cold packs to the extremity for the extreme pain as well as to decrease the local metabolism. A consultation by Dr. S. Silbert two days later corroborated the findings. The patient was then moved to another city where the condition became progressively worse with evidence of increasing intoxication. She died after one month. Autopsy was refused.

Laboratory examinations included a urinalysis which revealed an albuminuria with clumps of pus cells and a white cell count of 14,000 cells with 90 per cent polynuclear neutrophiles.

Comment. This case presents the typical picture of embolization due to rheumatic heart disease with auricular fibrillation. Pulmonary infarction occurred one month previously. The complete absence of all pulsations in both legs places the embolization at the bifurcation. But the symptoms and beginning gangrene of the right leg point to a complete occlusion of the right common iliac artery with partial obstruction of the left common iliac artery. Apparently there was a sufficient blood flow to prevent changes, despite absence of all pulsations.

Etiology

1. *Embolism* (50 per cent). The largest number of occlusions (seven cases) was due to embolism (table 2). All occurred in females ranging in age from 32 to 61 years of age (average age, 43 years) with the greatest number in the third decade of life. Without exception there were both a history and definite physical findings of rheumatic heart disease. In addition, all presented auricular fibrillation which caused emboli to be thrown from the left auricle to the aortic bifurcation. When the embolus itself was not large enough to occlude the aorta there undoubtedly occurred a more or less rapid antemortem thrombosis superimposed on the original nidus. Emboli were thrown off to other arteries in six of the seven cases. They were

Table II

	Male	Female	Total
1. Embolism (due to rheumatic heart disease with auricular fibrillation)		7	7
2. Thrombo-arteriosclerosis of aorta	4	1	5
3. Abdominal aneurysm with mural thrombosis		1	1
4. Infection		1	1
Total	4	10	14

the renal artery (three times), pulmonary artery (three times), cerebral arteries (two times) and the splenic, superior and inferior mesenteric arteries (once each). One unusually interesting case of embolization (H. M.) went on to recovery.

2. *Thrombo-Arteriosclerosis of the Aorta* (36 per cent). The term "thrombo-arteriosclerosis of the aorta" best indicates the underlying process of atheromatous degeneration and ulceration with superimposed thrombus formation. Five of our cases were in this category. The ages ranged from 50 to 80 years with an average of 62 years. The thrombo-arteriosclerotic group on the average were exactly 20 years older than the embolism group. However, the preponderance was among males in a five to one ratio. No more extensive occlusions throughout the aorta and its main branches occurred in this class than in the cases of embolism. However, occlusions of other arteries occurred more frequently in the embolic group than in the thrombo-arteriosclerotic group. In the former, other arteries were involved five out of six times. In the latter, only two out of five times. In one case (J. H.) a postoperative thrombocythemia was a secondary factor in the deposition of a thrombus since it began to form on an aorta that was markedly ulcerated by an atheromatous process immediately following operation.

3. *Abdominal Aneurysm with Mural Thrombosis* (7 per cent). It is a long accepted fact that in aneurysm of the abdominal aorta, death frequently results from a complete obliteration of the lumen by thrombi. An arteriosclerotic aneurysm just above the aortic bifurcation was found at autopsy in

a female of 84 years (A. W.). The Wassermann reaction was negative. There was hypertensive heart disease and a suggestive mass was palpated in the left lower quadrant. The gradually progressive thrombosis of the aneurysmal cavity became rapidly occlusive just prior to death.

4. *Infection* (7 per cent). In some infections, such as sepsis and typhoid, areas of degeneration may occur in the aorta. The intima or media is attacked and then acts as a focus for the formation of a thrombus. In one of our cases (H. T.) with a normal aorta and heart, bilateral iliopsoas abscesses secondary to a reticulum-cell sarcoma resulted in the formation of septic thromboses of capillaries in the periaortic tissues. This gave rise directly to an adherent thrombus. The aorta was not invaded by the malignancy. In addition, in inflammatory states there is a marked increase of the fibrinogen in the plasma and a decrease of the capacity of the blood to retain its corpuscles in suspension, thereby aiding coagulation. Essential thrombophilia as described by Nygaard and Brown [2] may conceivably, though extremely rarely, result in thrombosis of the aorta. It would be more likely to occur secondarily following splenectomy, or in polycythemia and myeloid or megakaryocytic leukemia.

Age-Sex Distribution

This condition occurred in all age groups past the third decade (table 3). In the younger age groups it has already been noted that the process was essentially embolic and occurred entirely among females. The thrombo-

Table III
Age-Sex Distribution

Age Group	Male	Female	Total
30–39		4	4
40–49		3	3
50–59	2		2
60–69	1	2	3
70–79			0
80–89	1	1	2
Total	4	10	14

arteriosclerotic group of aortic occlusions occurred in the older age groups and mostly among men (80 per cent). The case of abdominal aneurysm with mural thrombosis occurred in a female of 84 years, whereas the case due to infection occurred in a female of 39 years. The ratio of males to females in the entire series was 4 : 10.

Symptoms and Findings

The 14 cases were divided into a group of 10 cases which were diagnosed and four which were not diagnosed. The former group is considered first.

The latter group can be considered more appropriately under causes for errors in diagnosis.

1. *Pain.* The typical symptoms of severe sudden pains in the extremities occurred in eight of the 10 cases (80 per cent). The pain at times radiated into the lower back, inguinal regions, or girdle area. When present it varied in intensity from slight to severe, and was described as excruciating, sharp, stabbing, dull or aching. Varying degrees of shock ensued four times.

2. *Temperature and color changes* were present 10 times (100 per cent). The color changes were variously described as black, cyanotic, mottled, blanched, blue, pale or white. Temperature changes were referred to as cold or clammy. Rarely was superficial gangrene or bleb formation noted.

3. *Pulsations* were noted as being absent eight times (80 per cent). In one case (E. M.) pulsations were correctly noted as being absent as far up as the umbilicus. At autopsy, the aorta was found occluded at the level of the fifth lumbar vertebra.

4. *Weakness of extremities* was present six times (60 per cent) and varied from slight weakness to more frequent complete loss of motion or paraplegia.

5. *Loss of sensation* was noted six times (60 per cent). Occasionally, the sensations were increased early but later were completely lost.

6. *Reflexes* of the lower extremities were noted as absent four times (40 per cent).

Causes for Failure in Diagnosis

A correct diagnosis was not entertained in four cases. The reason for such failures rested simply on the complete absence of any signs or symptoms pointing to occlusion of the aorta or blood supply of the extremities. This can be explained on the rapid formation of an occlusive process shortly before death when painful stimuli were not prominent while thrombus formation was more rapid because of slowed circulation and other factors previously described. There was insufficient time for visible changes to develop in the extremities or the patients went into sudden shock or coma and died very shortly thereafter. One case (F. O.) with vomiting and right upper quadrant pain and tenderness was variously considered as mesenteric thrombosis, peptic ulcer, acute cholecystitis or acute appendicitis. There proved to be an embolus at the aortic bifurcation extending into both common iliac arteries. Another case (R. J.) which proved to be a thrombo-arteriosclerotic occlusion, suddenly became comatose and died two days later. Despite a previous thrombosis of the left middle cerebral artery, no signs nor symptoms were present referable to the acute occlusion. A male of 80 years, with bronchiectasis, on the chronic service for one and a half years, revealed a similar process terminally. The last case (A. W.) also presented no symptoms or findings in the extremities but had fecal vomiting with a suggestive mass in the left lower quadrant which was interpreted as a carcinoma of the

bladder or mesenteric thrombosis. The occurrence of other embolic or thrombotic phenomena should arouse suspicion of the possibility of aortic occlusion. Oscillometer readings and Landis-Gibbon tests may be helpful. Platelet counts, plasma coagulation time and hyperglobulinemia may be of value in suspicious cases. Roentgenographic studies of abdominal aorta calcification or aneurysm with or without contrast media may also shed some light.

Duration of Life

Following the onset of the acute condition, the duration of life ranged from six hours to one month. The average period was 10 days. One case (H. M.) with recovery was discharged from the hospital two months later. There was no apparent difference in the duration of life of the embolic and thrombo-arteriosclerotic groups.

Treatment

None of our cases was subjected to embolectomy. Most frequently the patient applied for treatment too late or after gangrene became apparent. In other instances, shock, circulatory failure or failure of diagnosis precluded surgical intervention. Large doses of papaverine and other vasodilators, with digitalization when indicated was the treatment of choice. The oscillation bed was in continuous use in two cases, with favorable results in one. The latter (H. M.) was also given continuous dry heat at 90° F., large doses of vasodilators (papaverine, aminophyllin and whiskey) as well as digitalization. Indirect ultrashort wave therapy was added later. She recovered two months after such intensive treatment. The use of heparin to mitigate a progressive occlusion might be of great value. Its use in occlusions of arteries and veins has already been well established. When a person to be operated upon is known to have marked arteriosclerosis (as in case of J. H.) it may be advisable to increase the water content in the blood by abundant drinking, or by administration per rectum, since an excessive concentration of plasma protein favors the inception of thrombi. A diet low in protein reduces the fibrinogen content of the blood. These measures are of added importance when there are indications of cardiac decompensation, especially of auricular fibrillation and a history of previous attacks of thrombosis or embolism elsewhere.

Summary

1. Occlusions of the abdominal aorta are highly dramatic episodes that are usually due to embolism from auricular fibrillation or thrombo-arteriosclerosis. The former condition is prevalent among women and in an age group averaging 20 years younger and is associated usually with embolic phenomena elsewhere. It also may be caused by abdominal aneurysm with mural thrombosis or by massive infection. Secondary hemic factors such

as essential or post-operative thrombocythemia, dehydration, increased fibrinogen and globulin, or pressure and trauma may exert an additional influence.

2. Symptoms and findings in the order of frequency are varying degrees of temperature and color changes, pain, absence of pulsations, weakness or paralysis of extremities, loss of sensations and absent reflexes.

3. The reason for failure in diagnosis is the rapid antemortem formation of complete occlusion with no time for the development of the characteristic signs or symptoms, especially when painful stimuli are decreased ante mortem or following shock.

4. This condition is compatible with life up until one month, although the average period of life was ten days.

5. The possibility of embolization to the aortic bifurcation should be anticipated in every case of rheumatic heart disease with auricular fibrillation occurring among females, especially when emboli to other organs have already occurred.

6. It is well to remember that in some cases of thrombo-arteriosclerosis of the aorta, symptoms and findings referable to the lower extremities may not be due to the more common peripheral vascular diseases but rather to a slow thrombotic occlusion at the bifurcation of the aorta.

7. A case is presented of a patient who recovered, under conservative management, by recanalization of a rider's embolus occurring as a result of rheumatic heart disease with auricular fibrillation; complete observations were recorded.

Conclusion

Occlusion of the abdominal aorta should be strongly suspected when there is a sudden onset of pain of varying intensity in the lower extremities and pelvis with temperature and color changes, sensory disturbances, and weakness or paralysis. This possibility becomes greater when occurring in females with auricular fibrillation due to rheumatic heart disease, especially when signs of embolization have occurred in other organs. An early diagnosis may result in cure or arrest by surgical intervention (embolectomy), heparinization or other appropriate medical measures described herein.

Addenda

Two additional, interesting cases of saddle embolus diagnosed ante mortem occurred since this paper was submitted for publication. Two new factors are added: in the first case embolism from syphilitic aortitis, in the second case embolism from mural thrombus of myocardial infarction.

M. J., 46 year old white female, was admitted with progressive pain and occasional numbness in both legs for several weeks. In the preceding eight years she had had four epileptic convulsions. About the same time, she developed ptosis of the right eyelid and a two plus Wassermann reaction was discovered. About eight years

previously she had suffered an attack of paralysis, numbness and coldness of both legs, requiring seven weeks of bed rest. No cyanosis was noted and it cleared spontaneously. One week before admission, she noticed weakness in the right knee which soon spread to the ankle. The leg became numb and the next day it became cold. Since then both feet were cold most of the time.

Examination revealed negative findings except for the extremities. The skin over both legs and lower abdomen was cyanotic and cold. Pulses were unobtainable in the legs. Complete anesthesia was present up to both knees. Blood pressure was 160 mm. Hg systolic and 80 mm. diastolic. A diagnosis of thrombosis of the abdominal aorta and syphilis was made. The patient became rapidly worse, dying two days later, despite supportive therapy.

Autopsy revealed the heart to be entirely negative. It weighed 300 grams. There were no thrombi or ulcerations or other lesions. However, a syphilitic aortitis of the thoracic aorta was present. At the junction of the arch and descending portions, there were three firmly attached, small mural thrombi. One and a half inches above the bifurcation of the aorta was a large antemortem clot which completely occluded the lumen of the abdominal aorta. It extended into both common iliac arteries for two inches. Final diagnosis was mural thrombosis of the arch of the aorta with syphilitic aortitis; embolization to the bifurcation of the aorta with superimposed thrombosis.

Comment. In this unusual case, mural thrombi formed on the syphilitic involvement of the thoracic aorta. Since the heart, pulmonary veins and wall of the abdominal aorta were negative, it is fair to assume that there must have been embolization to the bifurcation with slow occlusion by superimposed thrombosis. This case, occurring in a female, is exceptional in that it is characterized by the absence of heart disease with fibrillation.

A. D., a white unemployed male, aged 44, complained of weakness, more marked on the right side, and pains in splenic, heptic and renal regions. The past history was entirely negative except for an accident 10 years previously when he was struck on the head, with resulting right-sided weakness.

Examination revealed a white, obese male in no acute distress, with weakness of the right side of the body. The mental processes were somewhat dull. The right half of the body and left side of the face were partially paralyzed. Heart sounds were of poor quality, regular, rate 120 beats per minute. Lungs were clear on percussion and auscultation.

Laboratory studies included an electrocardiogram which revealed a recent anterior coronary occlusion. The white cells numbered 23,400 per cu. mm. with 89 per cent polymorphonuclears and 10 per cent lymphocytes. Urinalysis disclosed a specific gravity of 1.016 with a trace of albumin and a few red cells per high power field. The temperature curve ranged between 99 and 102° F. with a terminal rise.

He complained of sudden severe pains in the thighs. Two days before death his extremities became slightly cyanotic, cold and numb up to the mid-thigh regions. The day of death his pulse became rapid and irregular and he entered a state of shock from which he failed to recover. Final clinical diagnosis was recent coronary occlusion and embolization to the bifurcation of the aorta and old cerebral accident.

Autopsy revealed no external evidence of disease or trauma except for slight atrophy of the left side of the body. Both legs were involved in a marked purplish discoloration completely encircling the mid-thigh region of both legs, slightly higher on the right. There was no edema or gangrene. Upon opening the aorta, only slight atheromatous degeneration was found in the thoracic portion but somewhat more marked toward the bifurcation. At the bifurcation of the aorta was found a saddle

embolus which was moderately adherent. It was partially organized and extended down the right common iliac as far as its bifurcation into its internal and external branches. The embolus with very slight difficulty exposed a lustreless, discolored endothelium. The embolus was especially adherent in the right common iliac artery. The surface beneath the embolus was not unduly thickened and there was no evidence of any atheromatous degeneration beneath (figure 1). Numerous embolic infarctions of the spleen and kidneys were evident. The heart weighed 470 grams. On

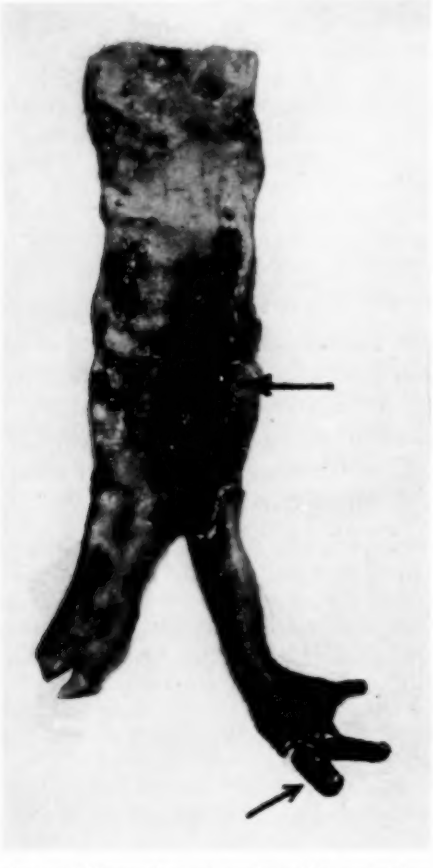

FIG. 1. Saddle embolus at bifurcation of aorta with extension into the right common, internal and external iliac branches. Although atheromatous plaques are noted, none was present beneath the embolus.

section the myocardium was soft, pale brown and on the left measured 2.5 cm., on the right 0.5 cm. At the apex of the heart was an adherent thrombus, the size of a walnut, which was gray and adherent to the anterior surface. The musculature beneath was thinned down sharply to 0.5 cm. in thickness and was discolored. The patch measured 6 cm. in diameter, involving the apex of the anterior surface and portions of the interventricular septum at the apex. The mouths were slightly contracted due to a fairly marked atheromatous degeneration about the sinuses of Valsalva. The coronary arteries were markedly thinned and sclerotic, being completely occluded approximately 2 cm. from the mouth of the left anterior artery. The pos-

terior coronary and branches were similarly sclerotic and narrowed but presented no evidence of thrombosis. The lungs weighed 1100 grams together. At the base of the right lower lobe, gray hepatization was present. In the ileum was a tremendous Meckel's diverticulum, measuring 12 cm. in length and 2.5 cm. in diameter. The brain was entirely negative.

Final diagnosis was recent myocardial infarction with superimposed mural thrombus of left ventricular apex, multiple infarctions of kidneys and spleen, saddle embolus of aorta and right common internal and external iliac arteries and early gangrene of both lower extremities.

Comment. This case is of special interest because the focus for embolization proved to be a recent myocardial infarction with embolization from the superimposed mural thrombus.

Following are two additional cases, both diagnosed ante mortem, with recovery in one on conservative management.

E. R., 84 year old white female, was admitted with complaint of sudden onset of blueness, coldness and pain in both lower extremities. She was semicomatose and further history was unobtainable.

Examination revealed absence of the right eye. The lungs presented moist râles, most marked in the left lower lobe. The heart was not enlarged but was fibrillating at the rate of 144 per minute. No murmurs were heard. The blood pressure was 160 mm. Hg systolic and 90 mm. diastolic. There was marked arteriosclerosis of all vessels. Both lower extremities were cold, mottled and cyanotic. Above the knees, however, the legs were warm and pink and the femoral arteries were definitely palpated. Diagnosis was thrombo-arteriosclerosis of the abdominal aorta and the popliteal arteries.

Laboratory studies included an electrocardiogram which revealed a 2:1 auricular flutter and left axis deviation. Chest roentgenogram presented marked calcification of the aortic arch and bronchopneumonia. Wassermann reaction was negative. Urea and creatinine were 81 and 3.1 mg. per 100 c.c. blood, respectively. Despite rapid digitalization and other supportive measures, the temperature rose and the gangrenous process progressed. Death occurred on the fifth day.

Autopsy revealed a markedly adherent, flattened, gray-red thrombus attached to a slight arteriosclerotic aneurysmal bulge, extending a distance of 6 cm. from below the opening of the superior mesenteric artery. The picture was typically that of thrombo-arteriosclerosis of the abdominal aorta. The abdominal aorta presented marked atheromatous degeneration with ulcerations. The mouths of the aortic branches were uninvolved. Both popliteal arteries contained two fairly recent emboli which had broken off from the aortic thrombus and completely occluded the lumina with resultant gangrene of the lower legs. In addition, there was arteriosclerotic heart disease and bilateral bronchopneumonia.

Comment. This case is of unusual interest because of the presence of both intravascular processes, thrombosis and embolization. The abdominal aorta was occluded by marked thrombo-arteriosclerosis which one finds in this age group. The lesion in the lower extremities was the result of emboli from this thrombotic area since they were not very adherent to the tibial arteries and were much redder than the abdominal thrombosis. Cardiac emboli due to fibrillation were ruled out at autopsy.

Despite cardiac arrhythmia, diagnosis was possible clinically because of the age, absence of murmurs, marked arteriosclerosis of all blood vessels

corroborated by roentgenogram, and bilateral gangrene. The most interesting feature, however, was the occlusive process in the abdominal aorta with embolization from this source. These skipped the bifurcation (absence of clot at this region and the presence of femoral pulsations clinically) and entered both popliteal arteries.

H. F., white unemployed male, aged 45 (case of Dr. Henry Wolfer) was admitted with excruciating pains in both legs of one day's duration. Paralysis, numbness and tingling of legs were also present. He had a history of rheumatic fever dating back 28 years. Nine years previously he developed infrequent attacks of epileptiform seizures. He had no edema, dyspnea or angina, but had exertional dyspnea for three years. An attack of right upper quadrant pain two weeks previously was diagnosed as ventral hernia, but operation was cancelled temporarily because of his cardiac condition.

Examination revealed a slightly obese male, somewhat apprehensive. The heart was slightly enlarged to the left with a presystolic murmur and thrill at the apex. There was no evidence of fibrillation and the rate was 80 per minute. Blood pressure was 150 mm. Hg systolic and 70 mm. diastolic. Lungs presented moist râles at both bases. There were no abdominal abnormalities noted other than a small ventral hernia above the umbilicus. Both lower extremities were cold from the midthigh to the toes. However, there was no gangrene and only slight cyanosis, indicating that the collateral circulation was still adequate. The right femoral artery was barely palpable and all other pulsations were absent. He was unable to move his legs. Diagnosis was rheumatic heart disease with mitral stenosis and saddle embolus to the aortic bifurcation.

Laboratory studies included oscillometry which revealed absent arterial pulsations below both knees and in the left thigh. The right thigh presented very weak waves. Electrocardiograms revealed sinus tachycardia with myocardial damage. Urea, creatinine and sugar were 32, 1.2 and 96 mg. per 100 c.c. blood, respectively. Urinalysis and blood studies were normal. Except for a rise to 103° F. on the third day, the temperature was always normal.

Therapy consisted of oscillating bed, an ampule of papaverine intravenously every four hours, 8 c.c. of heparin in a liter of 5 per cent glucose, intravenously. Heat was applied to the lumbar region. One week later the heparin was repeated and Buerger's exercises were added. General supportive measures, such as oxygen, hematinics and vitamin therapy, were added at intervals.

Course. One week later he was barely able to move his feet, but there was no cyanosis. One month later, he could move his right leg fairly well but his left leg moved only slightly with great difficulty. Six weeks later he was encouraged to try walking to aid further recanalization. Ten weeks later, his legs were warm and pink. No pulsations were palpable. This was expected since the collateral circulation, which develops after an occlusion of a major vessel, rarely, if ever, can be palpated or even measured oscillometrically. The oscillometer revealed only one-eighth in his left thigh. He entered the wheel chair stage after three months. Four months later, he developed an attack of pulmonary edema after straining at stool. This was relieved by phlebotomy. Five and one-half months after his attack he was able to walk about with great ease. Pulsations were still not palpable.

Comment. The presence of rheumatic heart disease with auricular fibrillation, the sudden onset of bilateral leg pains, numbness and paralysis, and the oscillometric findings all indicate the presence of saddle embolus. Collateral circulation and rapid recanalization produced adequate circulation.

It is difficult to evaluate the importance of heparin. In the other case, terminating in recovery, none was employed and recovery time was even shorter. However, when one views the tremendous mortality rate, every possible therapeutic agent should be employed. Perhaps further enlargement of the thrombus or embolism may be avoided. At any rate, its use should be encouraged in every case, since further thrombosis and embolism may thus be avoided.

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THE SIGNIFICANCE OF JOINT PAINS CAUSED BY STERILE STREPTOCOCCUS TOXIN *

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In 1937 Healey [1] reported that about 3 per cent of young adults being immunized against scarlet fever developed multiple joint pains as a reaction to one or more injections of the sterile filtrate of broth cultures of scarlet fever streptococci. She noted that the majority of persons who had this reaction gave a history of previous joint pains associated with rheumatic fever, or of streptococcus infections of the nose and throat. We had made similar observations. Healey showed that 74.6 per cent of a group of 63 such persons which she studied did not have joint pains when injected with the same dose of streptococcus filtrate which had been heated, and that 17.4 per cent had some joint pains but milder ones when given the heated material. Her conclusion was that the majority of such reactions were caused by the toxin in the filtrate rather than the protein of the streptococci or the culture medium.

Coburn and Pauli [2] studied in various ways 40 strains of hemolytic streptococci cultured from 38 rheumatic subjects during pharyngeal infections. About half were effective in reactivating the rheumatic process. The only constant characteristics of the effective strains were that they were stronger in streptolysin than the non-effective strains and that practically all produced toxin in broth cultures giving good skin reactions in dilutions of 1:50 or 1:100 in Dick positive persons.

The above studies prompted us to investigate the health performance of a group of student nurses who had multiple joint pains as a reaction to one or more immunizing doses of scarlet fever toxin. They were considered particularly suitable subjects because they are frequently exposed to hemolytic streptococcus infections. During the years 1934 to 1940, a group numbering 181 was found to have reported this reaction. Their health records were carefully tabulated. An equal number of nurses who were similarly immunized but reported no joint pains as a reaction to the doses were chosen from the records of each year as a control group. The results are tabulated in tables 1 and 2. It will be seen that the average period over which the health observation was recorded was well over a year per nurse in both groups. The average duration of time on duty was 83 days less per nurse in the "joint pain" group than in the control group. Many factors may enter into this difference but doubtless the most important was that

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TABLE I

Health Performance of Nurses Who Had Active Immunization Against Scarlet Fever

	Nurses Who Had *Joint Pain* as Reaction to Scarlet Fever Toxin (181 in group)	Nurses Who Had No *Joint Pain* as Reaction to Scarlet Fever Toxin. *Controls* (181 in group)
Total days of duty	86,597 (av. 478.4 per nurse)	101,546 (av. 561.0 per nurse)
Days off duty because of reactions to immunizing doses of scarlet fever toxin	451 (av. 2.5 per nurse)	107 (av. 0.6 per nurse)
Total days off duty due to illness	4,953 (5.7% of time on duty)	3,669 (3.6% of time on duty)
Days off duty due to respiratory infections including tonsillitis, pharyngitis, sinusitis, bronchitis, etc., but not including pneumonia	2,357 (47.6% of total illness). 166 nurses affected	1,825 (49.7% of total illness). 148 nurses affected
Days off duty due to "rheumatic fever," "rheumatic heart disease," "arthritis," "muscle pains," erythema nodosum	426 (8.6% of total illness). 28 nurses affected. Av. 15.2 days per nurse	145 (3.9% of total illness). 18 nurses affected. Av. 8.1 days per nurse
Number of nurses sent home because of illness	34 (18.8% of group)	19 (10.5% of group)
Number of nurses sent home because of rheumatic affections	17 (9.4% of group)	5 (2.8% of group)

TABLE II

Objective Evidence of Rheumatic Heart Disease in Groups Studied

	Nurses Who Had *Joint Pain* as Reaction to Scarlet Fever Toxin (181 in group)	Nurses Who Had No *Joint Pain* as Reaction to Scarlet Fever Toxin. *Controls* (181 in group)
Results of physical examination on entrance to training. Systolic or presystolic apical murmur, cardiac enlargement, ectopic beats	19	18
Number who presented evidence of progressive heart damage in association with attacks of rheumatic fever, arthritis or respiratory infection. (This evidence included in every case two or more of the following findings: premature contractions, auricular fibrillation, fresh cardiac murmurs, enlargement, prolonged tachycardia)	21	10

nearly twice as many nurses were sent home because of illness in the "joint pain" group as in the control group. It is interesting that 17 of the 34 nurses in the "joint pain" series who were returned to their homes because of illness were disabled by rheumatic affections, whereas only five of the 19 nurses in the control group who were sent home had rheumatic disease. Of course, the *total* time loss of these nurses is not recorded because they were not followed further.

It is seen that respiratory infections sufficiently severe to keep them off duty occurred in the majority of the nurses in both groups and accounted for nearly half the time loss from illness in both groups. However, the total time loss from them was greater in the "joint pain" group than in the control group. Rheumatic affections denoted by the diagnoses of "rheumatic fever," "rheumatic heart disease," "arthritis," "muscle pains," and "erythema nodosum" which in practically every instance were initiated by respiratory infections caused three times as much disability in the "joint pain" group as in the controls. As noted above, the *total* disability caused by these diseases is not indicated by the figures given because practically all of those diagnosed "rheumatic fever" or "rheumatic heart disease" were returned to their homes. The time loss due to other affections than those comprised in the respiratory and rheumatic groups was again in favor of the control group, but the difference was much less, the ratio being 2170 days in the "joint pain" group to 1699 days in the controls.

A history of "rheumatic fever," "rheumatic heart disease" or "arthritis" prior to coming to Cook County Hospital was four times as frequent in the "joint pain" group as in the controls. On the other hand, the history of previous attacks of tonsillitis was more frequent in the controls (64 times) than in the "joint pain" series (58 times). The experience with tonsillectomy had been practically the same, 107 (59.1 per cent) of the "joint pain" group having had their tonsils removed, and 110 (60.8 per cent) of the controls. In a large percentage of both groups tonsils had been incompletely removed.

That continuing infection was more common in the "joint pain" group than in the controls was evidenced by the fact that in routine cultures of the nose and throat to discover carriers in nurses on duty at Children's Hospital and on cultures in the nurses' infirmary, hemolytic streptococci were cultured 70 times in the "joint pain" group and 32 times in the control group.

The table on objective heart findings is self explanatory. The findings on physical examination are not considered by any means to be the only evidence of heart disease, but they are presented as recorded. Cardiograms were rarely made at that time. It is seen that the two groups were practically equal in the number who presented cardiac murmurs, irregularities of rhythm or enlargement, on entrance physical examination.

The figures on those having evidence of progressive heart damage in association with subsequent respiratory or rheumatic infections may be quite inaccurate. The discovery of a systolic murmur during the course of such infections in subjects in which a similar finding had not been recorded on the original physical examination was never taken as evidence of progressive heart damage unless it was found in association with one or more other significant findings such as pathologic arrhythmias, enlargement, persistent tachycardia, signs of decompensation, etc. It is seen that such evidence of progressive changes in the heart was twice as common in the "joint pain" group as in the controls.

Conclusion

Our observations support the view that a type of sensitiveness to hemolytic streptococcus toxin is present in a high proportion of persons who have had rheumatic infections or who harbor chronic streptococcus infections, which is not present in other persons. It is manifested by the development of joint pains when streptococcus toxin is introduced into their tissues. Such persons appear to develop rheumatic affections such as heart disease, polyarthritis and erythema nodosum more frequently than other persons not similarly sensitized.

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DUPLICATE MEASUREMENTS OF CIRCULATION TIME MADE WITH THE SACCHARIN METHOD *

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MEASUREMENTS of the velocity of blood flow, repeated at intervals on the same patient, are sometimes used to evaluate the treatment of congestive heart failure. It is obvious that such serial tests can be of value only if their results chiefly reflect changes in the degree of heart failure and are not materially influenced by other factors. That such extracardiac factors are operative has recently been proved by Lilienfeld and Berliner [1] who used alpha lobeline hydrochloride as an agent and found wide "spontaneous" variations in the results of duplicate measurements. The present study was undertaken to determine whether duplicate measurements of circulation time made with a more commonly used agent, saccharin, show similar variations.

Material and Method. Sixty patients were used in this study, 56 males and four females, ranging in age from 14 to 66 years. Twenty-six were patients suffering from various forms of heart disease; 16 of these showed signs of congestive heart failure. The remaining 34 patients showed no evidence of heart disease, but were suffering from the various conditions commonly encountered in a medical ward.

The saccharin test was performed twice on each patient, with an interval of one hour, during which the patient was at complete rest. The technic of the test as described by Fishberg, Hitzig, and King [2] was closely followed. Thirty-one duplicate tests were made under ordinary ward conditions; 29 duplicate tests, on the other hand, were made with the patients under so-called "basal" conditions, the patients being prepared exactly as for a basal metabolism test. In each case the results of the first and second tests were compared, and the difference was expressed in per cent of the first test. An example: first test 14.2 sec., second test 22.0 sec., difference 7.8 sec., or 54.9 per cent.

Results. The results of the duplicate tests are shown in table 1. They were identical or differed by less than 1 per cent in only six cases; in the remaining 54 cases differences varying from 1 per cent to 143 per cent (2 to 39 sec.) were found. In the majority (35) of the duplicate tests, differences greater than 10 per cent were obtained (table 2). The differences were greatest in the group of patients suffering from congestive heart failure, whereas in patients with heart disease, but without congestive failure, and in patients free from heart disease, the differences were generally of a lesser degree.

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Table 3 shows how the "basal" condition of the patient affected the differences between duplicate tests. In all three groups, non-cardiacs, cardiacs with heart failure, and cardiacs without heart failure, the variations between tests were markedly smaller than in the corresponding groups who were in non-basal condition, in other words, the results were more accurate; yet even in the basal group variations up to 55 per cent occurred.

It should be mentioned that the differences between tests varied in both directions: the second test yielded higher results almost as frequently (23 cases) as it yielded lower ones (31 cases).

TABLE I

Case No.	Diagnosis	Result of first test (seconds)	Result of second test (seconds)	Difference (seconds)	Difference expressed in per cent of first test
	I. Patients not in "basal" condition.				
	A. *Patients without heart disease:*				
1	Pneumonia	19.5	19.0	0.5	−2.6%
2	Gonorrheal arthritis	21.6	21.0	0.6	−2.7%
3	Cirrhosis of liver	14.5	17.0	2.5	+17.2%
4	Pneumonia	12.5	12.5	0	0%
5	Pneumonia	15.4	24.0	8.6	+55.8%
6	Infectious arthritis	13.5	15.5	2.0	+14.7%
7	Lung abscess	27.0	14.2	12.8	−47.4%
8	Peptic ulcer	14.8	14.3	0.5	−3.4%
9	Rheumatic fever without carditis	16.5	12.5	4.0	−24.1%
10	Pneumonia	16.5	17.0	0.5	+3.0%
11	Pulmonary tuberculosis	32.0	26.2	5.8	−18.1%
12	Pneumonia	18.0	23.0	5.0	+27.8%
13	Gonorrhea	28.4	20.4	8.0	−28.2%
14	Dry pleurisy	13.5	12.5	1.0	−7.4%
15	Pleurisy with effusion	12.1	14.2	2.1	+17.3%
16	Pernicious anemia	17.5	24.5	7.0	+40.0%
17	Peptic ulcer	16.0	17.3	1.3	+8.1%
18	Pneumonia	22.4	39.0	16.6	+74.1%
19	Malaria	18.3	24.2	5.9	+30.6%
20	Bronchiectasis	17.0	14.0	3.0	−17.6%
21	Gonorrheal arthritis	23.8	19.6	4.2	−16.9%
	B. *Patients with heart disease without heart failure:*				
22	Rheumatic carditis-heart block	20.1	18.8	1.3	−6.4%
23	Hypertensive heart disease	13.1	14.8	1.7	+13.1%
24	Hypertensive heart disease	21.0	31.0	10.0	+47.5%
25	Hypertensive heart disease	17.0	16.5	0.5	−2.9%
26	Hypertensive heart disease	18.0	17.5	0.5	−2.8%
	C. *Patients with heart disease in congestive heart failure:*				
27	Luetic aortitis	46.2	43.0	3.2	−6.1%
28	Hypertensive heart disease	27.0	65.5	38.5	+142.5%
29	Coronary sclerosis	24.5	32.0	7.5	+30.6%
30	Hypertensive heart disease	31.5	31.2	0.3	−1.0%
31	Coronary sclerosis	28.6	21.5	7.1	−24.8%

TABLE I (*Continued*)

Case No.	Diagnosis	Result of first test (seconds)	Result of second test (seconds)	Difference (seconds)	Difference expressed in per cent of first test
	II. Patients in "basal" condition.				
	A. *Patients without heart disease:*				
32	Pneumonia	17.6	17.7	0.1	+0.6%
33	Pulmonary tuberculosis	29.5	27.5	2.0	−6.7%
34	Pneumonia	16.8	16.8	0	0%
35	Peptic ulcer	30.4	31.8	1.4	+4.6%
36	Ulcerative colitis	14.2	16.0	1.8	+12.7%
37	Pneumonia	15.0	14.1	0.9	−6.0%
38	Pertussis	11.8	14.1	2.3	+19.0%
39	Pneumonia	14.2	22.0	7.8	+54.9%
40	Peptic ulcer	15.0	14.9	0.1	−0.7%
41	Pneumonia	19.0	19.0	0	0%
42	Pneumonia	20.6	17.6	3.0	−14.6%
43	Pneumonia	18.2	14.0	4.2	−23.0%
44	Sickle cell anemia	28.2	22.4	5.8	−20.9%
	B. *Patients with heart disease without heart failure:*				
45	Hypertensive heart disease	18.5	18.0	0.5	−2.7%
46	Coronary sclerosis	26.6	25.1	1.5	−5.6%
47	Coronary sclerosis	44.0	39.0	5.0	−11.4%
48	Rheumatic pericarditis	13.6	15.1	1.5	+11.1%
49	Rheumatic carditis	17.0	17.0	0	0%
	C. *Patients with heart disease in congestive heart failure:*				
50	Coronary sclerosis	27.8	25.0	2.8	−10.2%
51	Coronary sclerosis	31.2	21.0	10.2	−32.1%
52	Purulent pericarditis	29.0	33.0	4.0	+13.7%
53	Coronary sclerosis	22.0	21.0	1.0	−4.5%
54	Coronary sclerosis	24.0	29.0	5.0	+20.8%
55	Hypertensive heart disease	27.0	25.0	2.0	−7.4%
56	Luetic aortitis	19.0	23.0	4.0	+21.0%
57	Hypertensive heart disease	21.0	19.0	2.0	−14.2%
58	Hypertensive heart disease	19.0	23.0	4.0	+21.0%
59	Coronary sclerosis	20.2	19.3	0.9	−4.4%
60	Coronary sclerosis	34.0	25.0	9.0	−26.0%

COMMENT

An analysis of tables 1 and 2 shows that considerable differences between results of duplicate tests were the rule, and that agreement was the exception. How can these differences be explained?

Variations in technic undoubtedly accounted for minor differences in results. Special care was taken to make the technical conditions (gauge of needle, size of syringe, position of patient's arm) identical in each pair of tests. The injections, on the other hand, could not always be given with exactly the same speed, and the same vein could not always be used for both injections.*

* In the saccharin test, in which the bulk of the injected material is fairly large (nearly 3.5 c.c.), these factors will play a greater part than in the lobeline test in which minute amounts are employed.

Slight differences in technic, however, cannot possibly account for the major variations in results which commonly occurred in this study. There are other and more important reasons why duplicate measurements of circulation time may yield varying results, no matter what method is used. It is well to remember that the results of circulation time measurements made

TABLE II

60 Duplicate Measurements—Differences in Results of First and Second Tests, Expressed in Per Cent of First Result

No difference in results (or less than 1%)	Difference less than 10%	Difference less than 20%	Difference less than 30%	Difference less than 50%	Difference less than 100%	Difference more than 100%
6 cases	19 cases	15 cases	10 cases	6 cases	3 cases	1 case

with saccharin represent velocity of blood-flow plus reaction time. Variations in reaction time may have occurred among our patients; but if they did occur, they were unpredictable. It might, for instance, have been expected that the experience with the first test would cause a prompter response to the second test in a substantial number of cases; such "conditioning," however, was not reflected in our results, as the second circulation time was longer almost as often as it was shorter.

As regards the actual velocity of blood-flow, this velocity is, first of all, affected by changes in cardiac function. In our series, however, a short time

TABLE III

60 Duplicate Measurements—Average Per Cent Difference Between First and Second Tests

	Patients not in "basal" condition	Patients in "basal" condition
Patients without heart disease	21.8% (4.3 sec.)	12.6% (2.3 sec.)
Patients with heart disease, but without heart failure	12.5% (2.8 sec.)	6.2% (1.7 sec.)
Patients with heart disease in congestive heart failure	41.0% (11.3 sec.)	15.9% (4.1 sec.)

interval between duplicate tests was deliberately chosen so that marked changes in cardiac function were not apt to occur. Velocity of blood-flow is, of course, known to be influenced by numerous other factors, e.g., exercise, excitement, digestion, fever, basal metabolic rate, hemoglobin content, volume of circulating blood, vitamin B_1 deficiency, and pathological states of the vascular system. Certain of these factors may have been operative in our series, and may have caused changes in the velocity of blood-flow even though the interval between tests was short. An observation which supports this view is that patients in "basal" condition showed smaller differences between tests than those not so prepared. This observation leads us to the con-

clusion that the saccharin test should always be performed with the patient in a "basal" condition.

The literature on duplicate measurements of circulation time was recently reviewed [1] and, therefore, need not be discussed here. One point, however, deserves reëmphasis, namely, that duplicate measurements of circulation time show the greatest variations in patients suffering from congestive heart failure. This was found by several investigators,[1, 3, 4] and has been clearly confirmed by our own studies, as here reported. Among non-cardiacs and cardiacs without congestive failure considerable differences occurred occasionally, but the average difference between tests was definitely greatest in the congestive heart failure group. These differences were greater not only in seconds—which was to be expected—but were greater when expressed in per cent. The observation is of practical significance because circulation time tests are most frequently performed on patients suffering from heart failure; in other words: they are least reliable in the very cases in which they are most needed. The conclusion is clear that serial tests made with the saccharin method should not be relied on to evaluate the progress of a patient in congestive heart failure, unless the changes shown by these tests are marked.

Summary

1. Sixty duplicate measurements of circulation time were made with the saccharin method. The time interval between tests was always one hour.

2. Considerable differences between the results of the duplicate tests were frequently found. In only six cases were identical results obtained; in the remaining 54, differences varying from 1 per cent to 143 per cent (two to 39 seconds) were found. The result of the second test was higher almost as often as it was lower.

3. Thirty-one of the 60 duplicate measurements were made with the patients in "basal" condition. The differences between results of duplicate tests in this group were generally smaller than in the group of 29 patients who were not in "basal" condition.

4. The average difference in results of duplicate tests was greatest in patients suffering from congestive heart failure.

Conclusions

1. The saccharin test should be performed with the patient in a "basal" condition.

2. Serial circulation time tests with the saccharin method should not be relied upon to evaluate the progress of a patient in congestive heart failure unless the changes shown by these tests are marked.

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GOLD THERAPY IN RHEUMATOID ARTHRITIS *

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The use of gold in the treatment of rheumatoid arthritis has become increasingly popular during the past 10 years. Since the original papers of Landé [1] and Pick,[2] and the subsequent, more extensive studies of Forestier,[3] numerous series of cases attesting to its value have been reported in both the European and American literature. A collective review has been published recently by Cecil et al.[4] In 1936 the use of gold was instituted in the arthritic service of the Wm. J. Seymour Hospital, Eloise, Michigan, and three years later it was introduced at Harper Hospital, Detroit, Michigan. During the early part of our experience with this form of therapy, favorable symptomatic results were obtained in many instances. After continued observation of these patients, however, relapses were frequently observed so that a different interpretation of our results became necessary. It seemed desirable, therefore, to continue our observations for a longer period of time before publishing our results.

The report which follows is concerned with an analysis of the results of gold therapy on 101 roentgenologically studied cases observed during 1936–1942. For an evaluation of the late results, a follow-up study on 81 available subjects of this series is included.

Description of Cases

Of the 101 patients of this series, 95 were white and only six were negroes. Sex distribution was about equal between males (52) and females (49). These patients ranged in age from 20 to 81 years, with 55 per cent over 50 years at the time therapy was instituted. Not included in the final analysis of therapeutic results are 35 additional patients who, for various reasons, did not complete a full course of treatments. Seventeen of these discontinued treatment voluntarily; in 18, therapy was interrupted because of toxic reactions which will be discussed below.

All cases included in this clinical analysis have been classified into three groups according to the severity of the arthritic process. (a) In the *mild group* are included 14 patients (13.8 per cent) in whom the disease was confined to the periarticular soft tissue structures, with very little or no bony change demonstrable by roentgenogram. With only one exception, this entire group of patients was ambulatory. (b) In the *moderately advanced* group (30 cases—29.7 per cent) the joint disease was more extensive; some destruction of cartilage and limited ankylosis were present in several instances. Eight of this group of patients were bedfast. (c) Among the

* Received for publication July 21, 1942.

severe cases are included 57 patients with multiple joint involvement and extensive ankylosis and deformity; roentgenographic evidence of marked decalcification of the bony structures of one or more joints and loss of the intra-articular space was present. In this group are included three cases of ankylosing spondylitis with associated involvement of the peripheral joints. Two patients with "mixed arthritis" are also included. Ninety per cent of the patients of this group were bedfast, many for years in the same institution.

Gold Treatment

Gold sodium thiomalate (myochrysine) was used in 91 patients and gold thio-glucose (solganol-B oleosum) in 10 patients; gold sodium thiosulphate was used in two cases to complete courses started with myochrysine.* The sodium thiomalate and thio-glucose preparations were given intramuscularly; gold sodium thiosulphate intravenously.

The *dosage* of myochrysine varied throughout the six year period covered by this report. During the earlier part of the study 100 mg. were given weekly for a total of 18 to 20 weeks; subsequently, this dosage was given twice a week in a limited number of patients. In 1940 this was reduced to 50 mg. per week and more recently the dosage was further diminished to 25 mg. In most instances the latter dose was given twice weekly. The total amount of gold sodium thiomalate administered in one course has, therefore, varied from 0.5 gm. to 4 gm. Gold thio-glucose was given in ascending amounts starting with 10 mg. twice weekly and increasing successively to 25, 50, and 100 mg. until 1.2 grams were administered in a total of 21 injections. After an interval of two to six months a second course was given in about two-thirds of the cases; 40 patients received only one course, all others receiving from two to six courses. The total dose of drug administered varied from 0.5 gm. to 9.0 gm.

Other Treatment

More than one half of the patients in the series were confined to bed in the hospital at the time therapy was started. Most of these remained in bed throughout the first course. Physiotherapy consisting of baking and massage was given to most patients at some time during the course of gold therapy. It should be emphasized that these treatments were given so infrequently as to preclude any significant effect on the course of the disease. Focal infection, whenever present, was eradicated routinely before aurotherapy was instituted. Such therapeutic measures as vaccines, sulphur, vitamin D, and bee venom were given to a few patients before gold therapy was started. In each case, sufficient time had elapsed to nullify any effect which might have resulted from these measures. Artificial fever therapy

* Myochrysine was withdrawn from the market for a short period of time by the manufacturers.

was given to three patients between courses of gold. Analgesics, consisting principally of salicylates with occasional small doses of codeine, were used when necessary. Orthopedic measures such as traction, supporting splints, wedging casts and molds were used in a limited number of cases requiring such corrective procedures. More radical surgical interference, such as manipulation and various joint operations, were also used in several cases.

Precautions Observed during the Administration of Gold

Because of previously emphasized dangers of chrysotherapy, frequent observations were made for the appearance of untoward effects. The following routine was established: (1) frequent inspection of skin and mucous membranes; (2) urinalyses at weekly intervals; (3) hemoglobin determination, erythrocyte, leukocyte and platelet counts at weekly intervals in most cases; (4) icteric index determinations. Gold therapy was discontinued whenever toxic effects were indicated by these reactions, although in several instances it was resumed after apparent recovery.

Toxic Reactions to Gold

Some form of toxic reaction occurred in 38 per cent of all patients who were started on gold therapy. Except in one instance in which the patient received 25 mg. of gold sodium thiomalate, all toxic reactions observed followed the administration of large doses.

Dermatitis. A skin reaction of some degree was observed in 30 cases (25 per cent). This varied from simple erythema to extensive papulosquamous eruptions involving the entire body. Severe exfoliative dermatitis was not observed. In two instances the skin lesion consisted solely of a fine desquamation of the eyelids. Pruritus was frequently present without an associated rash, though in the absence of the latter, therapy was not discontinued. All eruptions seen, with one exception, occurred in patients receiving gold sodium thiomalate. The rash appeared not later than after the fifth injection in over two-thirds of the cases; in 10 of these it occurred before the fourth. It appeared during the first course in all but two instances and reappeared in a subsequent course only once. In most instances it lasted not longer than two weeks although in one patient it recurred intermittently during a period of four months. The minimum amount of drug administered before the development of the rash was 50 mg. In three-fourths of the cases this did not exceed 500 mg. In the past two years, during which very small doses of gold were given, dermatitis developed in only one case. Residual pigmentation of the skin after complete clearing of the rash has not been observed. Histological study of the erythematous skin showed dilatation of the capillaries in the papillary layer with associated edema and infiltration by lymphocytes, plasma cells, and histiocytes. Psoriasis, present in three patients, was not considered a contraindication to the administration of gold, although a definite exacerbation of this condition was observed

shortly after starting the drug. Alopecia occurred in one case after the patient had received approximately one gram.

Mucous membrane lesions, consisting principally of superficial ulceration of the buccal mucosa, occurred in four cases. In two of these the lesions persisted for several months after stopping solganol B, and were followed later by glossitis of several months' duration. Conjunctivitis occurred in three cases; in one there was an associated facial edema. A "metallic taste" was noted by one patient and bronchial irritation (gold bronchitis) by two.

Albuminuria. Minute amounts of albumin were found in the urine at some time or other during the course of therapy in approximately one half of the patients. There was no other evidence of renal irritation or damage in these cases. Significant amounts of albumin, however, were found in the urines of four patients. In all of these there was clinical evidence of nephrosis. In one the albuminuria developed during the early part of the second course of gold sodium thiomalate and disappeared completely nine months after its first appearance. In another patient the albuminuria is still present although there is no blood pressure elevation, edema or azotemia; the serum proteins are low. A third patient with albuminuria had an advanced rheumatoid arthritis and marked avitaminosis. He received 18 injections of myochrysine and returned approximately one year later with albuminuria, hypoproteinemia and a reversal of the albumin globulin ratio; the urinary sediment and blood urea were normal. This patient subsequently died, and at autopsy the kidneys showed amyloid disease. Microscopic studies were not made. In the fourth patient, the albuminuria occurred after two courses of gold and was associated with granular casts in the urine, peripheral edema, hypoproteinemia, normal blood urea, normal kidney function tests and a normal blood pressure. The albuminuria disappeared completely and recurred two years later following the development of fatal streptococcal endocarditis with septicemia. At autopsy the kidneys showed chronic pyelonephritis and amyloidosis.

Blood Changes. Anemia. Some degree of secondary anemia was present in most patients before the institution of chrysotherapy. When this was extensive correction with transfusions and other anti-anemia medication preceded the administration of gold. Following the use of large doses of gold the anemia became more marked in most cases. On the contrary, when small doses were used, a definite improvement in the blood picture resulted. Although most of the patients with an anemia received iron simultaneously, this improvement with small doses of gold was also noted in the absence of any anti-anemic medication in many instances. We are unable at present definitely to explain this effect of gold. It may act as a stimulant to the hematopoietic system of the body; when iron is also used, it may exercise a catalytic action not unlike that attributed to copper.

Eosinophilia. Eosinophilia exceeding 5 per cent was found in 11 cases; in five of these it exceeded 10 per cent. One patient developed an eosinophilia of 90 per cent with an associated rash and delirium following the fifth

injection of gold (500 mg.). Bone marrow studies in this case also revealed a marked eosinophilia. In a second case the eosinophilia was accompanied by granulocytopenia and a cutaneous eruption. Skin or mucous membrane lesions were found associated in four additional cases manifesting eosinophilia. In the remaining patients, no other associated toxic manifestations were noted. We were unable to substantiate the observation made by Sundalin that a high eosinophilia was always associated with a low sedimentation rate.

Agranulocytosis. This condition was observed in one case of our series. It occurred after the administration of only 300 mg. of gold, and was associated with a rash. The granulocytopenia persisted intermittently for five months with ultimate recovery. This patient had an allergic diathesis with a sensitivity to such drugs as aspirin.

Thrombocytopenia. Thrombocytopenia developed in three patients, one of whom died. In the latter an extensive subdural hematoma and multiple petechial hemorrhages were found throughout the body at autopsy.* In the second case of purpura a thrombocytopenia (19,300 platelets), high fever, joint swelling and a monocytosis (22 per cent) followed the administration of 500 mg. of gold sodium thiomalate. The latter was discontinued, and after the subsidence of the acute reaction the platelet count returned to normal and there was a complete restoration of the joints to normal. The third patient developed purpura with a moderate thrombopenia at the end of the second course of gold sodium thiomalate (1800 mg.), although a similar amount of gold given in the first course did not result in either of these toxic effects. After withdrawal of the drug, the purpura subsided and the platelet count returned to normal. Two years later, gold therapy in small doses (10 mg. twice weekly) was resumed, and after the eighth injection the platelet count dropped to 74,300 without purpuric manifestations. This promptly returned to normal after therapy was discontinued. One month later large doses of vitamin K (synkamin) were started in an attempt to prepare the patient against further thrombopenia. After four months, small doses of gold (10 mg.) were again resumed and were given in conjunction with synkamin. At the present writing, no further thrombocytopenia has developed.

Miscellaneous Reactions

Diarrhea and abdominal cramps were experienced by 10 patients. In none of these was there evidence of bleeding. Jaundice was never observed. In rare instances, a sense of precordial discomfort was experienced following the injections, and in one patient a true anaphylactic reaction with stenocardia and marked anxiety developed immediately after the intramuscular administration of only 25 mg. of gold sodium thiomalate. The subsequent injec-

*This was one of the first patients treated by us. The significance of the purpura unfortunately was not recognized and the drug was not immediately discontinued.

tion of very small and gradually increasing doses in this case resulted in marked clinical improvement without further reaction.

A few patients experienced temporary increase in joint pains and stiffness. In two instances, transitory blurring of vision was noted. The so-called "nitritoid" reactions, characterized by vertigo, giddiness, flushing of the face and headache, were observed in varying degrees in most patients treated during the year 1940. Since these reactions are now observed very infrequently, it is assumed that they were related to the quality of the product available at that time.

Results

The results in the present series are recorded in table 1. The *mild cases* all received at least one course of gold, five receiving two or more courses.

Table I

Severity of Arthritis	Total No. Cases	Initial Result			Relapses	Follow-Up Study			Rehabilitated
		Imp.	Questionable Imp.	No. Imp.		Permanent Imp.	No. Imp.	No Follow-Up	
Mild.....	14	13	0	1	3	11	1	2	4
Moderate .	30	24	4	2	11	18	8	4	11
Severe....	57	23	8	26	17	13	30	14	7

Improvement was noted in all symptoms, notably pain and stiffness, in all but one of these cases (93 per cent). An improvement in the general well-being of the patients was also observed. The only bedfast patient in the group became ambulatory. Relapse after the first course occurred in three patients. In one of these a second course was given with a resulting prompt remission of the symptoms.

A follow-up study was made on all but two of the mild group (table 2). The original improvement noted was found to persist in all at this follow-

Table II

Follow-Up Study

Distribution According to Interval after Treatment

Time Interval after Treatment	Mild	Moderate	Severe	Total Cases
1 yr.....	8	14	6	28
2 yr.....	1	3	6	10
3 yr. or more.....	3	9	31	43
No follow-up.....	2	4	14	20
Total.....	14	30	57	101

up examination. The four patients who were formerly incapacitated had returned to work. The status of the remainder was unchanged. Since only one year has elapsed since the termination of therapy final conclusions concerning the value of gold treatment in this group cannot be drawn.

In those classified as *moderately advanced,* one-third had more than one course of injections. Eighty per cent of the entire group experienced improvement following one or more courses. In four other patients the improvement was only slight or questionable, and in two no benefit was noted. All eight patients who were bedfast became ambulatory. Three of the four patients who required a cane were able to discard this support after completing therapy. Relapses occurred in 11 of the patients who had originally improved. Of the latter, eight had remissions following a subsequent course. The remaining three failed to have a remission.

A follow-up study was possible in all but four of this group. Of all cases originally showing definite improvement 78 per cent continued to show this improvement at the time of the check-up examination. No patients became worse. Eleven returned to a gainful occupation after having been previously incapacitated. Ten who had never been incapacitated, continued with their usual activities after receiving treatment. The remaining patients, although showing definite improvement, had not returned to active work at the time of the follow-up study. Since the final observation was made after only 12 months of therapy in only half of these patients, we consider it premature to draw final conclusions regarding the efficacy of gold therapy in this group.

In the *severe* advanced cases definite improvement was observed following one or more courses in 23 cases (40 per cent), whereas in eight the improvement was only slight or questionable. Twelve of those who were improved had previously been bed-ridden. In the remaining group (45 per cent) no improvement was noted at any time. Relapses occurred in 90 per cent of all cases that had previously showed some degree of improvement.* Nine of the latter have since had remissions following subsequent courses whereas eight have failed to improve. Although some in the far advanced group noted an alleviation of joint pain, the principal improvement experienced was that of increased joint mobility.

A follow-up study was made in all but 14 of this group, three of whom had died. The original improvement noted was found to persist in 13 (56 per cent) of those who had experienced definite improvement after completing treatment. Two patients, neither of whom had ever noted a marked improvement, were definitely worse at the time of the follow-up study. Seven patients (12 per cent) were totally incapacitated by their illness. Two of these later had a relapse which again temporarily incapacitated them. None of the other advanced cases was able to return to active work while under our observation. Since the follow-up studies in this advanced group were made after an interval of more than two years in most of the patients, the observed effects of therapy are considered to have real significance.

Combining all three groups of patients, there was noted a definite improvement in 60 per cent. This figure checks closely with the improvement rate of 66 per cent of Hartfall et al.,[6] 70 per cent of Forestier,[7] 66 per cent

* In four cases information relative to relapses was not available.

of Cecil et al.[4] and 61 per cent of Smyth and Freyberg.[8] Twenty-nine per cent of our cases showed no improvement at any time. Two patients became definitely worse. Twenty-one patients were released from bed confinement; 22 who were incapacitated returned to work.

Relapses occurred in 55 per cent of all cases showing an initial improvement. We are in agreement with Cecil that most relapses come on two to three months after cessation of therapy. For this reason we believe that careful and frequent observation following the cessation of therapy is important in order that relapses may be avoided or checked in their incipiency by another course of gold. It has not been our experience that relapses are usually milder than the original attack as reported by Cecil.

Comment

A satisfactory evaluation of any form of treatment for rheumatoid arthritis is admittedly difficult. The variable course of the disease with its natural tendency to spontaneous remissions makes hasty conclusions regarding the effectiveness of any therapeutic agent inadvisable. Thus, in a recent publication Short [9] recorded that 53 per cent of a series of 300 arthritic patients treated in the Massachusetts General Hospital during the past ten years experienced more or less satisfactory improvement after receiving nothing but "general therapy." Because of the danger of relapse, the calculation of results immediately after the completion of therapy is inadvisable. It is well known to all who have observed arthritic patients that a reactivation of the process may occur in the joints of patients at any time, even after years of quiescence. Prolonged observation is, therefore, essential in order that permanency of results may be assured. The follow-up studies in this series were made to avoid premature conclusions regarding gold therapy.

Satisfactory means for measuring small degrees of improvement in arthritic patients are not available. We made numerous attempts to measure changes in joints by means of a goniometer, and to determine the strength of the patients' hands as an index of improvement, with a dynamometer. Although there was noted slight change in some of the patients, neither method proved sufficiently satisfactory to continue their use. Because of the lack of an adequate index of progress, comparison of results with those published elsewhere is difficult. It is necessary to distinguish between limited subjective improvement which frequently follows bed rest alone, and an unmistakable change in the condition of the patient resulting in complete rehabilitation. Between these two extremes are various degrees of improvement. Thus, there may result an increase of only 10 per cent flexion in a joint, enabling the patient to perform some simple, though important, function which was not previously possible. To the patient this is an unmistakable improvement, and should be so construed, and yet socially and economically the patient is no better. In like manner, the patient may become ambulatory as a result of improvement in the joints of the lower extremities, and yet be unable to earn

his own living because of advanced deformities in the upper extremities. The difficulty of evaluating progress is obvious. The *ideal* criterion for recovery would seem to be the complete restoration to social and economic independence rather than the simple relief of symptoms in any one joint.

The sedimentation rate has been used by most clinicians as an index to the severity of the disease and as a criterion of improvement. Although it reflects the clinical course in many cases, we are at present unable to share the enthusiasm of many concerning the value of this test. Thus, we have observed patients with clinically active arthritis whose sedimentation rate was within normal limits. In other cases there has been a complete subsidence of the acute process for many weeks during which time the sedimentation rate remained persistently elevated. We have not used the sedimentation rate as a criterion for a continuation of gold therapy as recommended by Forestier.[10]

The classification of our patients according to the extent of the arthritic process was considered necessary in order to give a fair estimation of the effect of the drug. Failure to do this in some of the series recorded in the literature undoubtedly accounts for much of the variation in the improvement rates found. Series made up predominantly of early cases with little or no joint destruction would be expected to have higher improvement rates than those comprised largely of bedfast or wheel chair patients in an institution. The unusually good results recorded in the mild cases of this series, and the much less satisfactory results among our advanced cases illustrate this fact. Despite the low incidence of rehabilitation in the latter group we are still of the opinion that gold therapy is worthy of a trial in these human derelicts. In spite of their incapacitation, relief from pain and stiffness is very gratifying to them.

We agree with the observations made by Smyth and Freyberg [8] that the clinical results are just as satisfactory with small doses of gold (50 mg. weekly) as those obtained with larger ones. If this is true, there would seem to be no justification for using the latter.

The potential toxicity of gold compounds makes their indiscriminate use unwise and dangerous. Careful observation for early indications of toxic effects is essential, and when the necessary clinical and laboratory observations cannot be made, gold should not be used. The pathogenesis of these reactions is not known, but their occurrence after very small doses early in the course of treatment, in most cases, suggests a sensitivity reaction or an idiosyncrasy to the drug rather than a simple intoxication by a heavy metal. This theory has been advanced by others.[5, 11] The absence of toxic reactions in some of our patients who received as much as 5 to 9 grams of gold over a four to six year period further substantiates the former view. Thus, 19 of our patients received a total of from 5 to 9 grams of gold, and only six of these had a mild toxic reaction (rash) at some time during their therapy. In one additional case a mild diarrhea occurred. No *serious* complication was ever observed in this group of patients. We have at no time observed

normal sedimentation rates in patients with toxic reactions as reported by Ellman and Lawrence.[12] Inasmuch as we have observed practically no toxic effects since using very small individual doses, we are forced to conclude either that the amount of gold given in each dose has some effect on the production of a sensitivity reaction in patients, or that we have been recently using a less toxic and more highly refined preparation. We are inclined to favor the former view. We are unable to agree with Sundalin [5] that large doses are no more toxic than small ones.

The exact mode of action of gold in arthritis is unknown. Hartung and Cotter [13] have recently reported that serum from patients with atrophic arthritis becomes bactericidal against a strain of hemolytic streptococcus when treated with gold. Since the rôle played by this organism in rheumatoid arthritis is now questionable the applicability of this theory to human arthritis is somewhat doubtful. The development of rheumatic nodules *during* the course of gold therapy in six of our cases would indicate that chrysotherapy does not prevent the development of new rheumatic tissue.* This evidence mitigates against the bacteriostatic theory of Hartung and Cotter. Another explanation for the mechanism of the action of gold lies in its stimulating effect on the recticulo-endothelial system. This theory has been advanced by Kling, Saskin and Spanbock.[14] Evidence for this is not complete. A third possible mode of action lies in its effect on the water metabolism of the body. In recent studies by Jacobson, Leichtentritt and Lyons,[15] the effect of water loss from periarticular tissues was observed following diuresis by ammonium chloride and mercupurin. A profound improvement in the joint symptomatology, i.e., pain, stiffness and swelling, was demonstrated. It is suggested that gold in suitable combinations may produce a similar though less striking diuretic effect, with a resultant loss of tissue fluid and a consequent improvement in joint symptomatology.†

Conclusions

1. Gold is an effective remedy for the treatment of rheumatoid arthritis, aiding in the alleviation of all joint symptoms and effecting rehabilitation in a significant percentage of patients.

2. Aurotherapy should be limited to rheumatoid arthritis, and is most effective in the early stages of the disease. It is also frequently effective in relieving pain and stiffness in advanced cases, and is therefore worthy of a trial in these patients.

3. Careful and repeated follow-up observations should be made before drawing final conclusions about this therapeutic agent, since there is a high incidence of relapse and remission in the natural course of rheumatoid arthritis.

* A detailed report of these cases will be submitted for publication in the near future.

† Studies on the water metabolism of arthritic patients receiving gold therapy are now in progress at the Wm. J. Seymour Hospital.

4. Gold is a toxic drug and should be used only by those having experience with it. Careful observation for the early appearance of toxic effects should be made in all patients receiving this form of therapy.

5. The toxicity is probably the result of individual drug sensitivity rather than due simply to heavy metal intoxication. The administration of such large amounts of gold (7–9 gm.) as reported in this paper without the development of toxic reactions would tend to support this contention.

6. The exact mode of action of gold is not known. The observations herein recorded concerning the development of rheumatic nodules during its administration would seem to mitigate against the bacteriostatic theory advanced by Hartung and Cotter.

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SOME LEGAL ASPECTS OF HEART DISEASE AND THE ELECTROCARDIOGRAM *

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I. Nature and Volume of American Litigation Involving the Heart

The advent of comparatively inexpensive portable electrocardiographic machines has greatly multiplied the number of tracings being made in the practice of medicine, and the uses and abuses now seen by cardiologists will be secondarily reflected in court proceedings. We intend in the present paper to consider some of the pervasive problems regarding the use, value and shortcomings of electrocardiograms as evidence.[1] As a preliminary step, it would seem wise to consider the nature and source of cardiac litigation, and certain legal principles which orientate the problem of proof.

Most cases which come before legal tribunals are terminated in the trial court, where no statistics are kept that enable one to compare the incidence of various types of law suits. Workmen's Compensation Commissions in the larger industrial states, however, for some years have been issuing statistical analyses of claims, and these often disclose valuable comparative information regarding mode of accident and nature of injury suffered.

A certain percentage of cases are carried on appeal to higher courts. Such cases are disposed of by decisions supported by written opinions, which are printed and preserved as precedents.

It is evident from a survey of appeal litigation that a continuing flow of cardiac cases is going through the courts. Most of these are workmen's compensation cases; most of them result from some lifting, straining, or unusual exertion in the course of work, rather than from direct trauma; and most of them are disasters suffered by persons already afflicted with heart disease. Careful study of Workmen's Compensation statistics leads to the inference that, even in this more active field, injuries to the heart constitute a very small fraction of total claims.

The following legal categories are the main ones which may be expected to give rise to cardiac litigation:

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[1] How the electrocardiograph works is explained for the lawyer in Riseman, J. E. F., Principles of electrocardiography, 15 Rocky Mt. L. Rev. (April 1943) ——. The present paper is a specially adapted and more ambitious version of Smith, H. W., and Riseman, J. E. F., Applied use of the electrocardiogram in legal proceedings, 15 Rocky Mt. L. Rev. (April 1943) ——.

(1) *Tort law:* If A intentionally or negligently exposes B to an injurious stimulus causing cardiac injury or disability, this will afford grounds for liability in damages. The injured person may recover for medical, hospital and nursing expenses; for pain and suffering; for loss of earnings; and for any other items which the law allows in an effort to afford just compensation for the injury, including future as well as past effects.

Example: *Tort Case: Acute dilatation of heart in 11 year old boy allegedly caused by electric shock.*

B, an 11 year old boy, received a high voltage shock as a result of C Public Service Company's negligent failure to safeguard its lines from contact of children known habitually to play around and on one of the towers. In an action by B against C for negligent injury, B's doctor testified that "in all cases of severe electric shock there is a dilatation of the heart." He also testified that he had found, both by clinical examination and roentgen-ray pictures, that the plaintiff was so affected, and would be permanently. The jury returned a verdict in B's favor for $33,000. Affirmed on appeal.

Wolczek v. Public Service Co. of Northern Ill., 342 Ill. 482, 174 N.E. 577 (1931).

It is held generally that a plaintiff may recover damages for substantial aggravation of a preëxisting complaint, but not for that portion of the disability which existed before the accident and was not caused by it. It is obviously difficult for the medical man to estimate what portion of the final disability should be attributed to the accident and what portion to preëxisting disease or impairment. At present this segregation is not being carried out by all expert witnesses, and there is a regrettable tendency on the part of both counsel and witness to attribute the full disability to an accident, even though part of the complaints already existed.

(2) *Workmen's Compensation claims:* If employee A suffers injury from an *accident* arising out of and in the course of employment, and his employer carries workmen's compensation insurance, A is entitled to receive such benefits without proving any negligence or fault. The medical man must realize that the workman cannot recover if he is unable to prove the occurrence of an "accident." This involves application of legal interpretation to facts presented by testimony. As in all civil litigation, one who seeks to prove a necessary fact must establish it by a preponderance of the substantial evidence. It must appear that the accident was a *probable* substantial cause of the disability. No award can be entered if at the end of the hearing it appears from all the evidence that the proof of causal connection is conjectural. Testimony that the accident "might" or "could" have been the cause is too conjectural, standing alone, to prove causation. The fact that an accident could have caused an injury does not prove that it did, but the better court decisions hold it is competent as evidence of "probable" causation, if coupled with other evidence excluding the operation of all other possible causes capable of producing the injury.

Doctor's rôle in proof-making: The doctor's province as a prospective expert witness is to examine the claimant and determine the following facts:

(a) Is A suffering from a cardiac disability, and if so, does it involve partial or total incapacity, and is it temporary or permanent in character?

(b) Considering the history of the alleged accident, was the stimulus described adequate to cause the cardiac injury? Is such a mechanism of injury recognized scientifically—i.e., is there scientific warrant, in light of medical facts now known, for giving a professional opinion that the described stimulus *could* cause the alleged result?

(c) Considering the described stimulus, the symptomatology and the medical findings, and eliminating other possible causes by the orthodox differential methods required by good medical practice, can the expert give a professional opinion (perhaps based on a hypothetical question gathering together all relevant data) that the described stimulus probably *did* cause the described disability? A particular medical witness is entitled to give a "might" or "could" opinion as proof that such a sequence is scientifically possible, but the *plaintiff* will need to tender other evidence that the accident was a probable substantial cause without which the injury would not have occurred.

Failure of commissions to partition disability between accident and preexisting causes: Here again, there is not a very scientific handling by commissions or courts of the partitioning of disability between accident and preexisting causes. This opens up a realm of legal discussion and of social policy too broad for treatment in this paper.[2] It must suffice to say that most commissions and courts take the view that the employer accepts the idiosyncratic or impaired employee as he is, and if the latter becomes disabled by virtue of an accident which would not have injured the average person, the disability is nonetheless compensable. So long as this principle of compensation prevails, the doctor will be required to say whether the accidental stimulus or trauma was a probable substantial cause of a lesion appearing for the first time or of the aggravation of a preëxisting lesion, and to what extent the workman is and will be disabled.

Workmen's compensation claimant must prove an "accident," but this term is liberally construed so that extraordinary physical stress or strain, or nervous shock, not normally incident to the employment, is considered to be an "accidental" cause of any resultant injury.

Cardiac disasters which occur in industry usually befall workmen already subject to heart disease. To establish a compensable claim they must necessarily prove that the condition was substantially accelerated or aggravated by an accident arising out of and in the course of employment. If the employed workman suffers cardiac damage while performing ordinary tasks involving no more than usual stress and strain, the claim for compensation will fail for inability to prove "accidental injury."

[2] Regarding the proper measure of an actor's legal duty to idiosyncratic or hypersensitive individuals, see Solomon, H. C., and Smith, H. W.: Traumatic neuroses in court, Am. Jr. Psychiat., 1943, xcix (Sept.–Oct.); also, Cobb, S., and Smith, H. W.: Relation of emotions to injury and disease: A call for forensic psychosomatic medicine, ANN. INT. MED., 1943, xviii (Aug.).

Example 1: Blacksmith with chronic myocarditis suffered fatal coronary occlusion while shoeing horse; held (3–2 decision), reversing Board's award of compensation, that proof was lacking of sudden or extreme exertion and hence the injury was not "accidental."

La Fountain v. La Fountain, 21 N.Y.S.(2d) 193, 259 App. Div. 1095 (1940).

Example 2: A 58 year old warehouse laborer, who had long suffered from coronary sclerosis, was performing his accustomed task of pushing a truck over a slight elevation when he suffered a heart attack which totally and permanently disabled him. Held, vacating award of compensation and reversing Board and lower courts: The injury occurred in the normal performance of employment and there was no "accident."

Crispin v. Leedom & Worrall Co., 341 Pa. 325, 19 A.(2d) 400 (1941).

Example 3: Fireman suffering from preëxisting heart disease fought a fire in smoke and fumes for three hours and subsequently developed coronary thrombosis; held, vacating award of compensation and reversing Board and lower courts: Aside from question of causation, fighting fire is an ordinary incident of a fireman's employment, and the claim for compensation must fail for want of any "accident."

Brown v. City of Omaha, 141 Neb. 587, 4 N.W.(2d) 564 (1942).

Example 4: Where 56 year old laundry engineer suffering from preëxisting heart disease, collapsed from coronary occlusion, after painting boiler, held: Lack of any "accident" makes the injury noncompensable.

Siscoe v. Cooley (La.App.), 9 So.(2d) 313 (1942).

The courts hold that if the heart disability is due to some unusual exertion, strain, or lifting which is foreign to the normal work done in that type of employment, the effort is extraordinary and so may be treated as an "accidental injury," even though the exertion itself was intentionally made. This reflects perhaps somewhat of an extension of the concept of accident, but liberal construction of the compensation laws has resulted in these "overexertion" cases being treated in the same way as accidental falls or other unexpected mishaps.

Example 1: Carpenter with preëxisting heart disease collapsed and died after unusual exertions, on a very hot day, in carrying heavy pieces of lumber a block and a half, then up to a scaffold 18 or 20 feet above the ground. Held: A compensable accident.

Schneider v. Haerter, 119 N.J.Law, 548, 197 A. 281 (1938).

Example 2: Collapse and death of workman suffering from preëxisting heart disease, was a compensable "accident" where episode followed muscular exertion in using a heavy sledge hammer rather than the customary pick and shovel.

Bergagna v. Dept. of Labor and Industries, 193 Wash. 263, 91 P.(2d) 551 (1939).

Example 3: Fireman, who had preëxisting heart disease, sustained injury from carrying at one time three 27 pound tarpaulins up four flights of a burning hotel. Held: The injury was a compensable "accident" as the exertion was much greater than the usual or customary strains characteristic of his employment.

Brown v. Minneapolis Board of Fire Underwriters, 210 Minn. 529, 299 N.W. 14 (1941).

Example 4: Excessive exertion by 68 year old policeman in effecting arrest caused his death from preëxisting myocarditis; held: A compensable "accident."

Green v. City of Bennettsville, 197 S.C. 313, 15 S.E.(2d) 334 (1941).

Example 5: Sixty-three year old janitor, not shown to have been subject to preexisting cardiac disease, died suddenly from acute dilation of heart following unusual

exertion from extra work and longer hours moving furniture and stoking furnace in preparation for an entertainment. Held: A compensable "accident."

Fittro v. Industrial Commission, 377 Ill. 532, 37 N.E.(2d) 161 (1941).

(3) *War risk insurance:* The veteran must prove that he suffered a service-connected total and permanent disability before his policy lapsed for non-payment of premiums. It is not enough that he then had a partial disability which later became total and permanent. The courts do hold, however, that medical history subsequent to lapse of the policy is admissible evidence to show that in fact the assured was actually totally and permanently disabled when the policy lapsed. This is very helpful in psychiatric conditions where early stages of schizophrenia may be mistaken for a transient neurosis. Cardiac cases were comparatively infrequent in the war risk series after the last war, and because of careful screening by pre-induction medical examinations, they will probably be relatively infrequent after the present war.

(4) *Life, health and accident insurance:* If the assured, before applying for his policy, was suffering from heart disease and knowingly concealed this fact, the insurer may cancel the policy on the ground of breach of warranty or fraud, tendering back any premiums already paid. If the heart disease develops subsequent to the date of taking out the policy, from any cause whatsoever, the assured will be entitled to payment of benefits as provided by the terms of the policy. Here the main question which will arise for medical consideration will be whether the assured actually has heart disease, and whether it prevents his earning a living.[3] In this connection the doctor obviously must take into account the nature of the work for which the assured has training and experience, and on the basis of gainful employment thus open to the individual, say whether his cardiac condition will permit his working full or part time, or whether he has become totally and permanently disabled.

Many policies carry double indemnity provisions in case death occurs as a result of accidental means exclusive of disease. In such cases (in contrast to Workmen's Compensation cases), the accidental injury must have been the *sole* cause of the disability or death, and if preëxisting disease is a contribu-

[3] In 1937, a number of lawyers, doctors and laymen were brought to trial in the Federal district court of New York City for participating in a giant conspiracy to obtain payments on disability insurance by feigning heart disease. The *modus operandi* was quite interesting. Financially embarrassed policy holders, located and secured as clients by "runners," were coached by doctors and lawyers in the symptoms of heart disorder (particularly *angina pectoris* and *coronary thrombosis*), so that they could give impressive histories to unsuspecting general physicians. Some policy holders would simulate cardiac collapse in public places in order to be sent to hospital. Oftentimes the medical record was built up further prior to making claim by sending the coöperative policy holder for an electrocardiogram immediately after his heart action had been deranged by administering digitalis or other drugs. This scheme succeeded for several years, involved life policies amounting to more than ten million dollars in forty different companies, and resulted in payments and cash settlements of several hundred thousand dollars, before the conspirators became incriminated through increasing boldness and recklessness.

Hedley, O. F.: The fraudulent use of digitalis to simulate heart disease, ANN. INT. MED., 1943, xviii, 154.

tory cause the case falls outside the risk insured. If it can be shown that a preëxisting disease had become dormant but was excited into activity by the accident, most courts hold the accident to be the efficient cause of the disability and allow recovery of benefits. Many persons have been able to recover under accident insurance policies on this theory of arrested, or inactive preëxisting disease, exacerbated by accidental injury, and it makes no difference that the effect of the previous pathological process was to leave a weakened constitution more vulnerable to trauma.

Example 1: *Accident insurance: No recovery of benefits possible where preëxisting disease was a substantial cause of death; electrocardiograms used to prove progressive preëxisting disease.*

Action for death of an insured fireman, under an accident insurance policy which provided for payment of $2,000 to the beneficiary when the member "shall through external, violent and accidental means receive bodily injuries which shall independently of all other causes result . . . in the death of the member."

A 46 year old fireman was hospitalized on April 23, 1936, following a severe attack of angina pectoris. He drew disability benefits until June 24, 1936, when he returned to work, and electrocardiograms showed coronary thrombosis. On November 1, 1936, after lifting a ladder at a fire and lowering it to get under obstructing wires, he left the fire and was presently found dead on the running board of the fire truck. A jury found the death was accidental and returned a verdict for $2,000 in favor of the beneficiary of the accident policy. Medical evidence, including autopsy, showed that the assured died of angina pectoris, "a progressive and permanent disease in which attacks are provoked by emotion, excitement or physical exertion."

Held, on appeal: There could be no recovery for accidental death, for the angina pectoris was at least a concurring cause of the death.

Schroeder v. Police and Firemen's Ins. Ass'n, 300 Ill. App. 375, 21 N.E.(2d) 16 (1939).

Example 2: *Accident insurance: Strenuous efforts in loading wild horse, leading to symptoms of coronary thrombosis, from which assured had not previously suffered, was the accidental and sole cause of the subsequent death.*

X, an apparently healthy 50 year old employee of a land company, on July 23, 1938, undertook to load a wild horse into a truck. He worked and struggled with the horse for about two hours, and at times was dragged around by the horse. The exertion was so strenuous that X, the insured, was completely exhausted at the end of the struggle, complained of being tired, and when he went home declared that he was sick and went to bed. X had no supper that evening and he complained of pain in the region of the heart and in his left arm. He was nauseated and troubled with shortness of breath and sleeplessness. He remained in bed the next day, and thereafter was up and about, but unable to undertake any substantial work, and on August 16, 1938, he died of coronary thrombosis which doctors imputed to the tussle with the horse.

The beneficiary of an accident insurance policy carried by X sought to recover death benefits of $2,000 payable "If the Insured shall through accidental means, sustain bodily injuries as described in the Insuring Clause, which shall, independently and exclusively of disease, and all other causes, immediately, continuously and wholly disable the Insured from the date of the accident and result in death within 13 weeks."

Verdict and judgment for P for $2,000. Held, on appeal: Affirmed.

Jacobson v. Mutual Ben. Health & Accident Ass'n, 70 N.D. 566, 296 N.W. 545 (1941).

II. Nature of the Stimulus and Proof of Cause-Effect Relationship

It is an aid to the development of criteria in Scientific Proof, and conducive to better thinking, if we analyze cause-effect relationships in terms of mechanisms of injury. One phase of this process is to classify stimuli. The alleged injurious stimuli relied upon in legal claims for cardiac disability fall into four main groups:

(1) Direct trauma to the heart, including heavy impact injuries to the overlying thorax.

(2) Indirect trauma due to excessive demands made upon an impaired heart, usually consisting of some extraordinary lifting or straining, which could not be regarded as a normal task in that line of employment. This group includes, also, peripheral trauma at a locus so far removed from the heart that any effects on that organ are secondary.

(3) Exposure of the heart to noxious agents carried in the blood stream, such as carbon monoxide or other poisons.

(4) Injuries ascribed to what we may call psychosomatic stimuli, consisting of nervous shock without substantial impact, or of emotional upset, or of other psychic disturbances.

Effect of immediacy of cardiac injury on problem of proof; use of electrocardiograms as "completion evidence" to clarify existence of cause-effect relationship where stimulus is far removed in time from alleged consequential injury to heart:

Inspection of the law cases shows that a goodly portion of cardiac claims involve some specific stress or strain out of the ordinary, followed by speedy collapse of the workman. If the subject dies within seconds or minutes thereafter, the cause-effect relationship is more easily established. Time does not permit the making of electrocardiograms and the need for their use is not so pressing.

If, on the other hand, the collapse at work is followed by a period of weeks or months before the appearance of the final injury imputed to the stimulus, very serious problems of proof arise. In the first place, one who is subject to preëxisting heart disease has independent grounds for suffering injury, for cardiac decompensation may occur, particularly in far advanced cases, as a result of extraneous circumstances and even spontaneously. This time gap between stimulus and alleged response more than once has caused courts to deny compensation on the ground that proof of causation was speculative or conjectural.[4] It is in these cases where a long time interval

[4] Hawkins v. Powels Tillery Steam Co., Ltd. (Eng. 1911), 1 K.B. 988, 4 B.W.C.C. 178. (X, a 62 year old colliery worker, became sick at work ten minutes after finishing moderate exertions in pushing empty tramcars and died that night of angina pectoris. Held, vacating award: Since the medical evidence showed that angina pectoris attacks may be provoked by several causes, and the claimant did not rebut the possible operation of these, the proof of causation was too conjectural to permit a recovery of benefits. Timely electrocardiograms, made immediately after symptoms appeared, would have helped to resolve this ambiguity of causation.)

elapses between stimulus and alleged response that the electrocardiogram can render signal aid in many cases by providing what we call "completion evidence." By this we mean that the electrocardiogram may produce objective evidence immediately after the collapse and at intervals thereafter which will be of value in helping to prove or disprove the fact and continuity of causation. This application of the electrocardiogram involves the supplying of "bridging evidence" to fill in what may be a silent or ambiguous period between collapse at work and a subsequent final cardiac damage far removed in point of time.[5] It would therefore seem wise that all workmen who collapse in the course of their employment be hospitalized, and that initial and interval electrocardiograms be made. This can be done without risk of injury to the sick workman. These post-accident records are properly admissible in evidence, even though there be no pre-traumatic electrocardiograms for comparison. The post-accident electrocardiograms, in cases where they have any probative value at all (see table 1), constitute some circumstantial evidence, taken in conjunction with other examinations and findings, of the presence or absence of heart disorder. Clearly the strength of the electrocardiogram evidence is increased if pre-accident electrocardiograms are available to show condition of the heart prior to the alleged injury. Every workman who is to be employed for heavy labor should have such an electrocardiographic tracing made as a part of the medical examination at the time he is hired. This would involve no great expense and would serve to secure justice to both employer and employee. It may be that labor unions will need to espouse the systematic taking of electrocardiographic tracings in hospitals following collapse at work.

The physician as expert witness: Opinions based on personal knowledge of case and opinions based on hypothetical questions:

In the usual medico-legal case, the physician will be asked whether the described stimulus, in light of all available facts, was a probable substantial cause of cardiac disability or symptoms. He may also be asked to appraise the disability in terms of its restrictive effect on occupational and personal pursuits, and to give a prognosis as well as diagnosis.

The physician must approach his task of explaining and elucidating these problems with a realization of the grave responsibility which is his. He must refrain from testifying if he feels the subject is beyond his professional attainments; he must take properly into account the opinions held by leading cardiologists; he must avoid the naive error of assuming that disability

[5] This "completion use" of the electrocardiogram is strikingly illustrated in Brown v. City of Omaha, 141 Neb. 587, 4 N.W.(2d) 564 (1942). Plaintiff, a fireman, afflicted with preëxisting heart disease, filed claim for total and permanent disability. He alleged that his disabling coronary occlusion or thrombosis was an accidental injury received in fighting a basement fire for three hours on September 28, 1939, in the midst of dense smoke and fumes. Electrocardiograms made thereafter and up through November 29, 1939, showed that P had not yet developed coronary thrombosis. An electrocardiogram made on November 30 and December 1, 1939, furnished conclusive evidence of disabling coronary thrombosis. In view of this evidence, the Supreme Court of Nebraska held that the fire-fighting clearly was not a cause of the thrombosis and vacated an award made by the Board and affirmed by the lower court.

which follows an accident is necessarily caused by it; and he must present his findings and opinions in a simple, clear way understandable by a court and jury not likely to be accustomed to medical terms.[6]

Physicians testify as experts in two possible ways. If they have gained first hand knowledge of the facts of the case, the attorney will use the direct question and answer method to elicit this information and any final opinions deduced from it. It may happen that the expert has never seen or examined the subject whose grievance is the basis of litigation. In that event all material facts supported by competent testimony of others may be summarized in a hypothetical question addressed to the expert to evoke his expert opinion. If the doctor has been called to *treat* the patient, courts in most American states will permit him to relate symptoms which the patient described, even though such utterances of a third person fall within the technical definition of hearsay evidence. If, however, the doctor was called in only to examine the patient for purposes of testifying in court, most courts refuse to let the medical man testify as to the symptoms related by the claimant. This difficulty is not insurmountable; it can be met by the lawyer's putting the patient on the witness stand and having him relate his symptoms, and then incorporating the symptoms in a hypothetical question addressed to the doctor. This device makes it clear to the jury that the doctor has had to accept the patient's honesty in relating the symptoms, and that, in so far as history goes, he is adopting the statements of the patient.

III. Admissibility of Electrocardiograms as Evidence in Court

(1) *Physician who proposes to give an interpretation of an electrocardiogram must have his expert qualifications established to satisfaction of the court on preliminary or so-called "voir dire" examination.*

Since electrocardiographic tracings are not self-explanatory, but assume meaning only in connection with expert interpretation, they should not be allowed in evidence, nor should they be exhibited to the jury, without simultaneous proffer of a competent expert to explain their meaning and significance in relation to an issue in the case.[7]

If a lawyer proposes to use any witness as an expert, he must first establish his qualifications to speak on the proposed subject. This he will do by asking preliminary questions designed to satisfy the court that the witness by virtue of professional training, experience and familiarity with the literature of his subject, has acquired special knowledge and competency not possessed by the layman. The attorney will quickly interrogate the wit-

[6] One pressing need in medico-legal work is to avoid ambiguous terms; in the cardiac field this would include such ill defined diagnoses as endocarditis, myocarditis and acute dilatation. Courts should require pleadings to use accurate, specific terminology, for which see Nomenclature and Criteria for Diagnosis of Diseases of the Heart, 1940 (4th ed.), Am. Heart Assoc., N. Y.

[7] In Call v. City of Burley, 57 Ida. 58, 62 P(2d) 101 (1936), a personal injury case, a verified roentgenogram of plaintiff's pelvis was tendered without offer of any interpretation, and the court excluded it on the ground that "the average layman would get no information . . . unless the alleged fracture is pointed out and explained to him."

ness on such facts as his education, specialized training, experience, hospital affiliations and current practice. The general intent is not only to qualify the witness but to give him as much prestige and authority as his background deserves, and for that reason counsel usually goes further to inquire about important connections with learned societies, teaching and research activities, and particularly certification by specialized boards.

The lawyer for the opposing party has a right to cross-examine the witness to the end of showing that in fact he is not competent to appear as an expert witness. At the conclusion of the direct and cross-examination, the court will rule whether the witness is qualified as an expert or not, but this ruling may be reversed if during the course of trial it appears to the judge that the witness is in fact not qualified to give opinions on the subject in question.

It would be very helpful to courts in determining whether witnesses are qualified as experts, if the medical profession would devise some system of certifying what topics the given practitioner is competent to speak on by virtue of his attainments and field of concentration. This need is particularly keen in a field such as electrocardiography, where it is dangerous to lay down categorical norms of interpretation and much abuse may creep in if unqualified persons are allowed to rest extravagant opinions on particular tracings.[8]

[8] In future, many doubtful medico-legal claims involving the heart may be made on the basis of uncritical and extravagant use of the electrocardiogram if loose practices now current in the medical use of this diagnostic aid continue unabated. See Marvin, H. M.: Use and abuse of the electrocardiogram in medical practice, New England Jr. Med., 1942, ccxxvi, 213–217. The author comments on the unquestioned value of electrocardiography in such conditions as irregularities of cardiac rhythm, involvement of the heart during the course of systemic diseases, acute myocardial infarction, digitalis intoxication, structural lesions and the various types of cardiac neuroses. He feels, however, that much harm is being done, in the new widespread use of the electrocardiogram, largely as a result of the general practitioner's failure to recognize the following limitations on its value:

(1) Changes in the ventricular complex, including its terminal portion, have no special significance, with the exception of changes associated with myocardial infarction;
(2) The electrocardiogram hardly ever gives helpful information on the functional state of the heart, so that therapeutic questions of the amount of rest and action, and of the quantity of digitalis proper for the patient cannot be decided by the electrocardiogram;
(3) It is usually impossible to secure information about the prognosis from the electrocardiogram;
(4) The graphic records must be interpreted in light of clinical evidence;
(5) Many physicians are making unjustified diagnoses of heart disease solely on strength of minor variations in the electrocardiographic curves; these should never be accepted in absence of supporting clinical evidence;
(6) Misuse of the electrocardiogram is prevalent throughout the country;
(7) The American Heart Association has received a flood of letters from leaders in the cardiovascular field, asking for some board to establish certification of those physicians who are competent to interpret electrocardiograms. The primary intent would be to curb the present misuse of the electrocardiogram in the practice of medicine itself.

See, also, Willius, F. A.: A talk on certain prevailing fallacies in the application of clinical electrocardiography, Proc. Staff Meet., Mayo Clin., 1942, xvii, 137–140. The author attributes some of the main vices to:

(1) Naive assumption that fixed norms of interpretation can be employed automatically;
(2) Divorcement of electrocardiographic interpretation from clinical examination, re-

(2) *Predicate which proponent must lay in order to have electrocardiograms received in evidence.*

Whenever any special type of evidence is to be offered in court, certain preliminary steps must be taken to show that the apparatus and technic were adequate and trustworthy, and that the results tendered truly state the facts of the particular transaction. This is very important because errors, negligent or intentional, may creep in at many successive points in the acquisition of evidence, and it would be an imposition on courts if one who sought to use a species of evidence were not willing to vouch for its reliability.

In this process of "laying the predicate," the physician will be called upon to testify:

1. That the electrocardiograph machine was standard and adequate equipment in good working condition, and properly standardized.[9]

2. That the electrodes and leads (Leads I, II, III, IV) were applied in the conventional manner and that the usually accepted technics were used in procuring the tracing.

3. That the electrocardiographic tracings were made by the physician himself, or that they were made under his personal supervision and direction by a competent technician, and that he is willing to vouch for their accuracy.[10]

4. That the tracings were made on a sitting or recumbent patient whose heart action was not then affected by any exertion or drugs. The witness must be ready to affirm under oath that the electrocardiographic tracings are

sulting in errors of omission and commission since the electrocardiogram alone is not an adequate form of cardiac study;

(3) Failure of medical schools to provide adequate instruction in electrocardiography.

It goes without saying that this prevalent and growing misuse of the electrocardiogram is certain to be secondarily manifested in the courts of the land. The only safeguard is for courts to hold to the strictest standards of competency in testing a doctor's fitness to give an expert opinion or interpretation based on the electrocardiogram. Here signal help could be had from a "proficiency certificate" issued by the medical profession to those who propose to appear as electrocardiographic experts in legal proceedings. See Smith, H. W.: Scientific proof and relations of law and medicine, ANN. INT. MED., 1943, xviii, 450–491; Clinics, 1943, i, 1404.

[9] When the electrocardiograph is properly standardized, a current of one millivolt will cause a deflection of the beam of the string shadow equal to one centimeter.

[10] If the technician is available, ordinarily he should be called to court, unless counsel stipulate in advance that the electrocardiograms to be used have been properly made and may be offered in evidence by agreement without formality of laying a predicate. The technician should be charged with the duty of filling out a standard record each time an electrocardiogram is made and this should show the name and address of the patient, the hour and date, position of the patient, and presence of any significant circumstances such as taking of drugs or indulgence in exercise, etc. Such a record has three important uses:

(1) It may be used by the technician to refresh his memory before testifying;

(2) In case the technician is unavailable, the record may be admissible in evidence as an entry made in the course of business, thus bringing the facts recorded within an established exception to the hearsay rule;

(3) In some states, the record may be offered in evidence as a business entry without producing the technician, even though he is available locally.

free of artefacts and portray a true and accurate picture of heart action without distortion introduced by extraneous factors.[11]

5. That the tracing is identified as pertaining to the particular subject.

6. That the tracings have been in his care or under his supervision from the time the pictures were made until they are offered in evidence.

Proper practice is to offer the authenticated electrocardiogram in evidence before permitting any opinion to be given interpreting it.

The electrocardiograms, so verified and vouched for as trustworthy, should be offered in evidence before any opinion is expressed upon them. The courts and workmen's compensation commissions should refuse to permit opinion evidence as to electrocardiograms which are not first offered in evidence.[12] This may be rested on a proper application of the best evidence rule.[13] The original tracing has primary value, whereas a mere

[11] See Esler, James W., and White, Paul D.: The distortion of the electrocardiogram by artefacts, Am. Heart Jr., 1929, iv, 296–304; Hartwell, A. S., Burrett, J. B., Graybiel, A., and White, P. D.: Effect of exercise and of four commonly used drugs on the normal human electrocardiogram, with particular reference to T-wave changes, Jr. Clin. Invest., 1942, xxi, 409–417.

In the New York conspiracy to procure payment of insurance disability benefits for simulated heart disease, policy holders were given moderate doses of digitalis. This was done prior to electrocardiographic examinations to be made by unwitting cardiologists. Some patients were even surreptitiously "dosed" while in hospital. In some cases the drug produced only a flattening of the ST intervals. In others, varying degrees of auriculoventricular block occurred. Premature contractions were frequently produced and in a few instances actual inversions of the T-wave occurred. The net effect was to produce an electrocardiographic tracing suggestive of heart damage.

One insurance company doctor, after reading an electrocardiographic tracing so produced, said: "If the patient is not taking digitalis, I would say that he is totally disabled."

Another insurance company doctor said regarding electrocardiographic tracings submitted in support of a different insurance claim: "Since digitalis administration has been denied, it must be assumed that this record is associated with myocardial damage of coronary origin."

Hedley, O. F.: The fraudulent use of digitalis to simulate heart disease, Ann. Int. Med., 1943, xviii, 154.

[12] X claimed workmen's compensation for cardiac disability allegedly due to accidental injury suffered from exposure to carbon monoxide in a mine, but an arbitrator made an award for the employer, finding that X's disability was due to chronic myocarditis. Dr. Y testified favorably to the employer, basing his opinion partially on electrocardiograms not produced in evidence, and the claimant, on this ground among others, sought to have the award set aside for misconduct of the arbitrator.

Held: As in case of roentgen-ray plates, the electrocardiographic picture should be produced before an expert opinion is given interpreting it, but since a Kansas statute provides that "the committee or arbitrator shall not be bound by technical grounds of procedure or evidence," nor is erroneous admission of evidence mentioned in the statute describing what constitutes "serious misconduct," this departure from proper practice is not a ground for setting aside the award.

Lefebre v. The Western Coal and Mining Co., 131 Kan. 1, 289 P. 456 (1930).

Electrocardiographic tracings are fully as complicated as roentgen-ray pictures, and the better view is that the latter must be offered in evidence before an expert opinion is given interpreting them.

Marion v. Coon Construction Co., 216 N.Y. 178, 110 N.E. 444 (1915). (Cited with approval in the Lefebre case, supra.)

Neill v. Fidelity M. L. Ins. Co., 119 W.Va. 694, 195 S.E. 860 (1938). A less desirable rule is that the physician, on direct examination, may give his opinion based on interpretation of roentgen-ray plates without simultaneously producing them, and that the opponent, on cross-examination, may require their production. Sullivan v. Minneapolis, St. P. & S. S. M. R. Co., 55 N.D. 353, 213 N.W. 841 (1927).

[13] The court in the Lefebre case, supra, seemed to consider the vice of non-production of the electrocardiographic tracing to be an infraction of the hearsay rule. This analysis hardly

description of it involves inferior secondary evidence and a conclusion of the interpreter, which independent experts and opposing counsel cannot reasonably test or cross-examine unless they have opportunity for inspection.

Electrocardiograms are taken directly on photographic paper, so that there are no negatives to be produced at the trial. This practice minimizes likelihood of fraudulent retouching or alteration of tracings. As an additional safeguard, the court should require at least 4 to 6 inches of each lead to be offered in evidence. This would afford several repetitions of each given configuration, thus minimizing still further any slight risk of artefacts or intentional distortion.

IV. Persuasive and Probative Value of Electrocardiograms

It is a fact well known to trial lawyers that visual or demonstrative evidence has a strong persuasive appeal for lay jurors. The reasons for this are various: the immediacy of demonstration through the eye, the avoidance of ambiguity and abstruse presentation, and the dramatic appeal, all contribute to this phenomenon.[14]

It is by no means certain that electrocardiograms will enjoy the same degree of jury appeal as some other species of demonstrative evidence. This is because the tracings are too complicated to be understood by the lay juror, and he can only accept the expert's interpretation. In some jurors this may arouse a sense of antagonism and a reluctance to give the electrocardiographic evidence the acceptance one might expect. These complications, however, are somewhat counterbalanced by the strong logical appeal, as the juror is bound to realize that a visible record made at the time "tends to pin things down" more completely than the distant recollection of an auditory experience.

From the standpoint of probative value it is obvious that electrocardiograms in their proper sphere are of great value because they substitute objective demonstration of a uniform character for variable subjective impressions. Furthermore, the tracing provides a permanent record and eliminates dangers which attend reliance on memory in the giving of testimony.

All of us know from personal experience that there are few, if any, absolute facts. One of the pitfalls in proving anything is to dispose of alternative inferences which might be drawn from a body of evidence and lead to utterly different conclusions. In this respect, proof in law and science are no different. Whenever a physician is to testify in court regarding electro-

fits in with the customary and historical concept of the hearsay rule as a prohibition against offering unsworn verbal testimony of a third person not present in court. That the vice is in withholding the best evidence, is shown by the decisions which permit a doctor to give an opinion on a roentgen-ray picture, without producing the latter if proof first be offered that the picture is lost.

Stiles v. McLean, Finch v. McLean, 103 N.J.Eq. 537, 138 Atl. 119 (1927);
Vale v. Campbell, 123 Or. 632, 263 Pac. 400 (1928).

[14] Smith, H. W.: Components of proof in legal proceedings, Yale Law Journal, 1942, li, 537.

cardiograms, he must acquaint himself and his lawyer with the diverse conditions which might produce the same or a substantially similar electrocardiographic tracing. We cannot undertake here to give the electrocardiographic differential diagnosis on every conceivable medico-legal condition. But in the trial of a particular case, the expert witness must be prepared to do so. If he is called by the plaintiff he will want to do this to satisfy himself and the court that his diagnosis and consequent prognosis are trustworthy and probably correct, rather than conjectural. If he is advising the defense, he will expect the opposing witness to be held to the same scientific differential routine.

V. The Value and Shortcomings of Electrocardiography

The electrocardiogram may yield objective information, not obtainable by any other means during life, on three aspects of heart disease:

(1) It may give direct proof of the presence, location and type of an abnormal rhythm, even if no demonstrable changes are evident at post mortem.

(2) It may give direct evidence of the presence of damage to the heart muscle.

(3) It may yield indirect confirmatory or illustrative evidence of the presence of certain types of pathologic lesions or the action of certain etiological agents. This is true because some types of cardiac lesions (valvular, myocardial, pericardial or vascular) are frequently associated with certain electrocardiographic patterns, (e.g. left axis deviation in hypertension or aortic valvular disease) and some etiological agents are likely to result in specific types of cardiac disease (e.g. RS–T interval and T-wave changes in carbon monoxide poisoning or myocardial infarction).

The electrocardiogram, therefore, if positive, can be used to demonstrate that cardiac damage actually exists and in many instances it may yield confirmatory evidence concerning the type of damage. If electrocardiograms are taken at appropriate times (preferably before and at frequent intervals after the injury), they may show objectively that cardiac damage occurred following that injury and perhaps that the type of damage sustained was the type likely to result from that specific form of injury. Furthermore, it may be possible to infer that the type of cardiac damage illustrated by the electrocardiogram *may*, under certain conditions, result in cardiac symptoms or disability.

On the other hand, it is important to realize that it is impossible to state from the tracing alone that the alleged injury and nothing else resulted in the cardiac damage; or that the damage evidenced in the tracing necessarily resulted in cardiac symptoms or incapacity; or, where the electrocardiogram is normal, that cardiac damage or symptoms do not exist. This is true because most electrocardiographic abnormalities can occur in several different

cardiac conditions; furthermore, an abnormal electrocardiogram does not *necessarily* mean poor cardiac function; and, also, cardiac damage does not *necessarily* show itself in the electrocardiogram. It must be pointed out, also, that medical opinion is divided as to the causal relationships between certain types of stimuli (trauma not involving the chest wall, physical overexertion, fatigue, emotion, etc.) and cardiac damage or poor function.

VI. Use of the Electrocardiogram as Evidence

In general, it is unwise to rest the diagnosis of a heart condition on the electrocardiogram alone, but, rather, the tracing should be utilized as part of the total available clinical evidence. The electrocardiogram can be used to obtain objective confirmation or illustration in regard to specific cardiac problems, but since most electrocardiographic abnormalities can occur in several different cardiac conditions, and since cardiac damage does not *necessarily* result in electrocardiographic abnormality, the significance of the electrocardiogram in the *specific* instance must be interpreted by properly trained and experienced individuals.

It is obvious that the main use of the electrocardiogram is to present objective confirmation of the presence of heart damage, and the time relationship between the alleged injury and the development of the cardiac damage. This usually requires interpretation or opinion of the specific electrocardiogram in relation to the specific cardiac problem.

It is evident that the electrocardiogram does not have the same probative value in all instances. In general we may divide the applications of the electrocardiogram into four classes ranging from high probative value in establishing heart condition to absence of probative value. The several classes of heart conditions which conceivably may confront the examiner are presented in table 1.

Table I

The Relative Importance of the Electrocardiogram in the Diagnosis of Heart Disease

Etiology	Pathology	Function
Congenital III	Developmental Defects III	Congestive Failure IV
Rheumatic III	Valvular Damage III	Cardiac Asthma IV
Syphilitic III	Arterial Damage III	Angina Pectoris IV
Arteriosclerotic II	Muscular Damage	Limitation of Activity IV
Hypertensive II	A. Degeneration or destruction	Causes of increase of cardiac
Asthmatic II	of the myocardium II	symptoms:
Thyrotoxic III	B. Relative myocardial weak-	Increase in pathologic lesions IV
Pneumonic III	ness (especially in a heart al-	Increase in work IV
Diphtheritic III	ready damaged) IV	Abnormal rhythm I
Toxic II	Pericardial Damage II	Bacterial Endocarditis IV
Traumatic II	Abnormal Rhythm I	

I. Diagnosis may be made by the electrocardiogram alone (see text).
II. Diagnosis usually, or frequently, is confirmed or corroborated by electrocardiographic evidence.
III. Diagnosis may be aided by the electrocardiogram under some circumstances.
IV. Diagnosis is not helped by the electrocardiogram.

1. *Instances where the diagnosis may be made by the electrocardiogram alone.* Here the evidence has its highest probative value, and on occasion may be entitled to conclusive effect, as against contradictory findings made by less reliable methods. These cases include the arrhythmias, or departures from normal rhythm in the heart beat.

In many of these instances the diagnosis cannot be made without positive electrocardiographic evidence, and in most cases the diagnosis can be made by the electrocardiogram alone, even without clinical examination of the patient. The electrocardiogram, however, usually tells little about the *cause* of the arrhythmia or the *amount of disability* resulting from it. Its value, therefore, consists in providing objective demonstration that abnormal heart action has occurred. The circumstantial value of this evidence clearly is enhanced if a person who attributes heart disorder to accidental injury can produce pre-traumatic electrocardiographic tracings showing that the rhythm of the heart was normal prior to the alleged incident.

2. *Instances where the clinical diagnosis may be confirmed by electrocardiographic evidence.* This group includes conditions where changes in the heart muscle occur due to hardening of the arteries, high blood pressure, chronic asthma, poisoning, forceful injury, or progression of underlying disease.[15] In this group the typical textbook picture of the clinical condition usually includes a typical electrocardiographic picture. A positive electrocardiogram, therefore, is important objective corroborative evidence of the existence of the clinical condition. The electrocardiographic picture, however, may not be specific for the condition under discussion, and therefore, the tracings must be interpreted as part of the entire picture. A normal electrocardiogram, as we have mentioned, does not necessarily disprove the existence of damage. Failure to obtain adequate electrocardiographic studies of such cases suggests incomplete study unless there are extenuating circumstances.

3. *Instances where the cardiac diagnosis may be aided indirectly by electrocardiographic evidence.* In this third category (table 1, III), the conditions themselves are not identifiable by a characteristic electrocardiographic pattern, but they may result in various types of cardiac abnormalities which do have characteristic electrocardiograms. For example, rheumatic stenosis of the mitral valve may be associated with the electrocardiographic picture of right axis deviation, whereas disease of the aortic valve may be associated with the picture of left axis deviation. Here again a normal electrocardiogram does not disprove the existence of pathologic lesions.

4. *Instances where the electrocardiogram throws no light on the specific cardiac problem.* This group is of considerable importance for it deals with the impairment of cardiac function or disability for which compensation is sought.

[15] Some leading major works on electrocardiography are: Pardee, Clinical aspects of the electrocardiogram, 1941, 4th Ed., Paul B. Hoeber, New York; Graybiel and White, Electrocardiography in practice, 1941, W. B. Saunders, Philadelphia; Katz, Electrocardiography, 1941, Lea & Febiger, Philadelphia; Katz, Exercises in electrocardiography, 1941, Lea & Febiger, Philadelphia.

On the basis of available knowledge, it is possible to make certain suggestions concerning the use of the electrocardiogram as evidence of the state of the heart.

Since the electrocardiogram should be used only in relation to the entire clinical picture as developed by well rounded examination of the heart, it is wise to look askance at any testimony in which the electrocardiogram is relied upon as sole proof of the presence of symptoms or disability. This is true because a positive or abnormal electrocardiogram merely demonstrates the presence of cardiac abnormalities, and these may or may not result in symptoms or disability. We continue to stress this point because of the evident danger that courts might be led erroneously to accept an abnormal tracing, alone, as adequate proof of a major cardiac disability due to an alleged injury.

The following actual problems of cardiac disability coming before courts and workmen's compensation commissions illustrate type situations where electrocardiographic evidence might be of value.

Group I: *Direct trauma to the heart, including heavy impact injuries to the overlying thorax.*

It is generally accepted that direct injury to the heart or chest wall may result in damage to the heart.[16] Such damage will show itself in symptoms or signs of heart disease or dysfunction. Electrocardiograms may yield objective proof of the existence or development of cardiac damage following injury. The importance of taking such tracings at intervals appropriate to show the time relationships between the traumatic injury and the cardiac damage is evident.

Case 1: *Workmen's compensation insurance: alleged death from pericarditis.*[17]

[16] Master, A. M., Dack, S., and Jaffe, H. L.: The relation of effort and trauma to acute coronary occlusion, Indust. Med., 1940, ix, 359–364; Warburg, E.: Subacute and chronic pericardial and myocardial lesions due to non-penetrating traumatic injuries, 1938, Oxford Univ. Press, New York; Boas, Ernst P.: Angina pectoris and cardiac infarction from trauma or unusual effort, with a consideration of certain medicolegal aspects, Jr. Am. Med. Assoc., 1939, cxii, 1887–1892.

[17] The necessity for "education" of the lay jury and court in the medical problems involved is obvious in each instance. The description below is not meant to be a complete discussion of pericarditis, but rather a presentation of those aspects necessary for better understanding of the rôle of the electrocardiogram in such cases.

Pericarditis (inflammation of the outer surface of the heart) may be caused by local infection (pneumonia, tuberculosis, rheumatic fever); reaction to the toxemia of kidney disease (uremia); inflammation or damage to the heart (myocardial infarction); or direct injury with or without perforation of the chest wall. The diagnosis is based on:

(1) The finding of specific signs, especially a "friction rub" (a rough, grating, reduplicated sound synchronous with cardiac contraction and relaxation). This is usually accompanied by symptoms of heart damage (pain, rapid heart rate, etc.) plus signs of inflammation (fever, elevated white blood cell count, elevated sedimentation rate, etc.).

(2) Objective evidence in the electrocardiogram.

The electrocardiographic picture may have one of three general forms:

(1) A characteristic upward sloping of the RS–T segment seen in any or all of the four leads. This progresses rapidly (within days) to temporary inversion of the T-wave followed rapidly (within days) by return to normal.

(2) Progressive changes in the electrocardiogram, especially the RS–T segment or

X, a workman employed on a machine used to press copper bands around shells, fell on August 1, 1916, while carrying a load, and struck his chest on an iron lever. This caused pain and left a mark over his heart about five inches long. X received first aid treatment, and on being taken home that night went straight to bed complaining of pain in his left side and trouble in breathing. On the second day he came under care of physician Y, who testified that he found X suffering from pain in the left side of the chest in the region of the heart, with labored breathing, jerking whenever he took a long breath. He also found X's heart was laboring and heard an "abnormal sound" of the heart, and he testified that X's death in hospital on August 8, 1916, was due to "pericarditis" caused by the accident. X's past history showed no sickness except for a two week period a year previously, and he had worked steadily at general labor without any complaints about his heart or lungs. The employer insisted X did not die as a result of the accidental injury, but that his death was due to a disease, neither produced nor aggravated by such injury. Held: Death award made by Industrial Board affirmed.

Bucyrus Co. v. Townsend, 65 Ind. App. 687, 117 N.E. 656 (1917).

Comment: Was claimant suffering from cardiac disability? The plaintiff X obviously had cardiac damage as shown by the doctor's findings on August 2 and thereafter. The diagnosis in this instance rested on the clinical picture rather than on any tangible objective evidence. Properly dated and identified electrocardiograms might have shown the characteristic RS–T segment or T-wave changes proving objectively that pericarditis or myocardial damage occurred immediately following the alleged injury.

2. *Did the cardiac disability cause claimant's death?* This cardiac damage was the cause of death. The electrocardiogram would give no specific information concerning the severity of the disease or prognosis of the individual patient, but it is generally agreed that the outlook is not good for persons with the clinical and electrocardiographic picture associated with pericarditis, and death frequently results.

3. *Were cardiac disability and resultant death caused by an accident arising out of and in the course of employment?* The particular stimulus in this case was medically adequate to produce the injury. While it is true that other conditions might have the same electrocardiographic pattern, all the evidence proved that no other cause existed, and the blow on the chest was the actual cause. The electrocardiogram would give no evidence concerning the actual precipitating cause of the cardiac damage, but since the time of the accident was known and since medical attention was sought shortly thereafter, it would have been possible, by taking electrocardiograms at proper intervals, to show that in this particular instance the cardiac damage had the proper time relationship to all the relevant factual evidence, thus drawing all evidentiary data together faithfully into one mosaic.

T-wave, other than the specific upward sloping of the RS–T segment. *Obviously, to show the changes outlined in (1) and (2) the tracings must be taken at the appropriate times.*

(3) A normal electrocardiogram with no changes.

See Langendorf, R., and Goldberg, S.: The electrocardiogram in traumatic pericarditis, Am. Heart Jr., 1942, xxiv, 412–416.

Vander Veer, J. B., and Norris, R. F.: The electrocardiographic changes in acute pericarditis, Jr. Am. Med. Assoc., 1939, cxiii, 1483.

Case 2: Tort Case: *Recovery of damages for heart block attributed to heavy impact injury of thorax negligently inflicted by another.*[18]

A, owner of the ship *Italy Maru*, engaged in the lumber-carrying trade between west coast ports and Asiatic countries, hired B, a stevedore company, to load the vessel from railroad cars brought onto the docks. A also hired C, a middle-aged individual, to work between boat and car marking lots of lumber for their proper placement in the hold. Observe that C was not an employee of B; furthermore, since part of his work was aboard ship he was subject to maritime law rather than to the Workmen's Compensation Act of the State of Washington in respect to any injuries sustained.

B, in operating a loading boom, negligently brought a heavy timber against C as he was standing in a proper place on the railroad car. This serious injury occurred on February 11, 1922. The record does not show the interim medical history, but in the following November, C developed heart block, ventricular systole dropped to 32 per minute, and C became subject to fainting spells, so that he could not safely walk the streets without an attendant. Medical testimony was offered that C was totally and permanently incapacitated for gainful employment and that the heart block "either could be caused, or, if latent, could be rendered acute by the injury." A jury returned a verdict in favor of C against B, for $35,000, and on appeal judgment in this amount was affirmed.

McEachran v. Rothschild & Co., 135 Wash. 260, 237 Pac. 711 (1925).

Comment: Did a cardiac disability exist? It is evident that this workman C had heart block and this resulted in disability. The electrocardiogram would have furnished objective proof of the occurrence of heart block, even if postmortem examination revealed little. Indirectly the electrocardiogram would have helped prove the existence of cardiac disability due to heart block, for the clinical characteristics and fatal outcome of this condition are well known.

Was the cardiac disability caused by an accident arising out of and in the course of employment? This case illustrates the difficulties encountered when a long interval of time elapses between the alleged injurious stimulus and the alleged disabling result. Under such conditions every possible means of cardiac study should be used to prevent serious injustice to claimant or defendant. A single electrocardiogram would have been of little value in establishing a cause and effect relationship, for any abnormality observed might have antedated the injury, or might have resulted from natural aging

[18] Heart block is an abnormality of rhythm occurring physiologically when the usual rhythmical impulses which cause the heart to beat at the normal rate (about 72 beats per minute) are "blocked" or fail to stimulate the ventricles to contract. As a result, new impulses arise at a slower rate (about 30 to 40 per minute) from a new location.

This slow rate tends to reduce cardiac output of blood to a level insufficient to maintain normal physical activity. Furthermore, it is not uncommon for the heart to cease beating entirely or to beat erratically and inefficiently; as a result, loss of consciousness, convulsions and frequently death may ensue.

The causes of heart block are several and include age (arteriosclerosis), infections (syphilis, rheumatic fever), tumors, myocardial infarction, and damage due to trauma. In the latter case the heart block is likely to occur soon after the trauma but may be delayed in its appearance.

The electrocardiographic picture of heart block is typical and diagnostic. It consists of a complete dissociation between the usual impulses (P-waves) arising in the S–A node (which cause the heart to beat at the normal rate), and the new ventricular impulses (QRS and T-waves) arising in the A–V node or ventricle (which beats at the slow rate). The electrocardiogram tells little about the reason that the heart block has developed.

processes during the course of the illness and unrelated to the injury. Repeated interval electrocardiograms if obtained might, however, have shown the development of, or freedom from, interval cardiac damage.

Group II: *Indirect trauma, including peripheral injury.*

Such cases most commonly arise, as we have stated previously, in relation to Workmen's Compensation. The problem may also arise in tort cases where negligent or intentional acts cause peripheral injury culminating in cardiac disability.

Expert medical opinion will frequently disagree on the relationship between such overexertion, fatigue or indirect trauma and cardiac damage, especially if there is an appreciable lapse of time between the alleged incident and the cardiac result. Obviously, all means available should be pressed into service to obtain all possible objective data relative to the cardiac condition. These considerations make advisable initial and interval electrocardiograms, and possibly also hospitalization, for *all* workers who collapse in the course of their employment or shortly thereafter.

Case 3: *Workmen's compensation: angina pectoris and coronary thrombosis imputed to excessive strain from long hours of clerical work, without traumatic injury.*[19]

X, a 48 year old claim adjuster, subject to arteriosclerosis, worked progressively harder, day and night, for nine months. This was made necessary by the great increase in claims to be adjusted from about 100 per month (a full load for an adjuster) to about 250 per month. X became very fatigued by this excessive exertion. He also developed nervous strain as a result of constant complaints from his employer about slowness in settling claims. He became subject to frequent violent headaches, heartburn and fatigue, and on April 28, 1934, allegedly suffered an attack of angina pectoris, followed on May 5, 1934, by a coronary thrombosis which totally incapacitated him. The employer vigorously contended that there was no "accidental injury" arising out of the employment. A doctor testified that "My opinion is that excessive work and strain induced a premature change in his coronary system." He further testified that overwork, worry and emotional strain induced a spasm in a susceptible coronary artery and resulted in the disturbance of the vasomotor system bringing about angina pectoris. A Compensation Commission made an award. Held, on appeal: Affirmed.

[19] *Clinical Picture and Definition of Terms.* According to present concepts, angina pectoris (heart pang) occurs in persons whose arterial blood flow to the heart muscle (coronary circulation) is unable to respond adequately when additional blood is needed. When the *supply* of blood to the heart is inadequate for the *demands* of the heart muscle, a state of relative anoxemia (oxygen deficiency) results, and the patient experiences heart pain. The most common cause of such an inadequate coronary circulation is arteriosclerotic narrowing of the coronary arteries. The most common causes for precipitating attacks of angina pectoris are exercise and emotion. With cessation of the precipitating exercise or emotion, the discrepancy between demand and supply of blood ceases, the physico-chemical changes secondary to anoxemia reverse themselves, and the pain disappears. Under conditions of physical or emotional fatigue, attacks of angina pectoris may occur more frequently.

If anoxemia persists for a sufficiently long period of time (due to complete occlusion of a coronary artery or to prolonged angina pectoris), the physico-chemical changes become irreversible and permanent damage to the heart muscle occurs. This destruction of heart muscle is called *myocardial infarction.* Since it is due usually to coronary occlusion or coronary thrombosis, these terms are frequently used interchangeably.

The electrocardiographic picture of myocardial infarction is quite typical. It consists in most cases of changes of the RS–T segments and T-waves progressive over days or weeks; in other instances, transient arrhythmias may indicate involvement of the ventricular muscle. Since these changes are transient and progressive, tracings should be taken soon after the onset of the illness and frequently thereafter.

The circumstances leading up to injury were equivalent to overexertion or excessive muscular strain in a day laborer, and the disability was therefore compensable as an "accidental injury."

Hoage v. Royal Indemnity Co. (Ct. of App. D.C.), 90 F.(2d) 387 (1937).

Comment: Was the claimant suffering from myocardial infarction and angina pectoris? Because of the typical clinical and electrocardiographic picture of myocardial infarction there should be no difficulty in showing that this occurred. The problem is quite different in angina pectoris for here there may be no clinical or electrocardiographic evidence of heart disease, even though the condition is advanced and there is marked incapacity.

Since angina pectoris is usually due to coronary arteriosclerosis, about one half of the patients may show one or more of the many electrocardiographic abnormalities seen in this condition, but about one fourth of the patients may show no evidence indicating heart damage.[20] Recently, attempts have been made to utilize the electrocardiogram during or after exercise or during generalized anoxemia (induced by breathing an atmosphere poor in oxygen content), as a test for the presence of coronary insufficiency. There is no uniformity of opinion, however, concerning the practical value of such studies. Levy et al.[21] and Masters et al.[22] believe that a positive result is of value, yet Riseman et al.[23] have shown that these changes are so rapidly progressive that tracings cannot be taken under conditions permitting comparison, and, furthermore, that the difference between the response of normal subjects and those with heart disease may be so slight that the test may be of little practical value in those borderline or controversial cases where further evidence is most needed.

The problem of incapacity due to angina pectoris frequently raises problems under clauses of insurance policies which promise benefits and waiver of premiums during disabilities. In those cases of alleged incapacity from angina pectoris where the insurance company has demanded electrocardiograms and found them negative, this obviously is not proof positive of nonexistence of that disease, and the inquiry will need be broadened to gather all lay and clinical evidence available concerning the nature of the complaint. If electrocardiograms are positive, the insurance company may be aided in coming to a more speedy recognition of the merits of the claim. It is interesting to note that electrocardiograms are becoming increasingly important in the conduct of the insurance business, both in respect to appraising

[20] Riseman, J. E. F., and Brown, M. G.: An analysis of the diagnostic criteria of angina pectoris, Am. Heart Jr., 1937, xiv, 331.

[21] Levy, R. L., Bruenn, H. G., and Russell, N. G.: The use of electrocardiographic changes caused by induced anoxemia as a test for coronary insufficiency, Am. Jr. Med. Sci., 1939, ccxli, 241; Patterson, J., Clark, T., and Levy, R.: A comparison of electrocardiographic changes observed during the anoxemic test on normal persons and on patients with coronary sclerosis, Am. Heart Jr., 1942, xxiii, 837.

[22] Masters, A. M., Friedman, R., and Dack, S.: The electrocardiogram after standard exercise as a functional test of the heart, Am. Heart Jr., 1942, xxiv, 777.

[23] Riseman, J. E. F., Waller, J. V., and Brown, M. G.: The electrocardiogram during attacks of angina pectoris, its characteristics and diagnostic significance, Am. Heart Jr., 1940, xix, 683.

the risk in regard to elderly or doubtful subjects applying for insurance, and in determining the merits of claims for benefits.[24]

To what extent, if any, did claimant's heart condition disable him? The incapacity due to heart disease is clear in this case from the clinical history. The electrocardiogram would throw little light directly on this or any other specific instance, although it is generally agreed that coronary thrombosis is frequently followed by incapacity for doing work which was possible previously.

Was cardiac disability caused by an accident arising out of and in course of employment? It is generally agreed that attacks of angina pectoris in susceptible individuals are more common under conditions of fatigue, overexertion or emotional strain. There is considerable difference of opinion as to the causal relationship between such stimuli and the precipitation of coronary thrombosis. Routine electrocardiograms throw no light on this problem. In each instance, therefore, the final expert opinion must rest upon skilled and informed judgment applied to the whole mosaic of evidentiary data.

Group III: Exposure of the heart to noxious agents carried in the blood stream, such as carbon monoxide or other poisons.

Case 4: *Workmen's compensation insurance: death from endocarditis allegedly accelerated by inhaling carbon monoxide gas.*[25]

X, an individual long subject to endocarditis, was a repair man in an automobile shop. Early in 1920 he went to work in the test shed where a number of cars were being tested constantly with engines running. During his work in this test shed, from time to time he was affected by the gas and went outside for relief. In particular, upon June 4, June 14, and June 22, 1922, he had experienced this trouble. On June 14 he left his place of work, went outside and was dizzy and faint. He was taken home, returned to work upon the 19th, worked about two days and on the 22nd again suffered from the effects of the gas or his heart trouble, and thereafter did not return to work. X died on October 4, 1924, of endocarditis. Claim was made for death benefits. The case had a protracted course before the Industrial Board and the New York courts, with an award finally being entered in favor of X's legal representatives on the theory that accidental carbon monoxide poisoning operated to cause death by substantially accelerating preëxisting endocarditis. The trial court found that: "The progressive and active condition of endocarditis, from which the deceased died on the 4th day of October, 1924, was naturally and unavoidably the result of the inhalation of carbon monoxide gas at his employer's test shed on June 14, 1922. He had a preëxisting condition of the heart and the disturbance caused by the toxemia, or poisoning, which in this case was produced by the inhalation of the said carbon monoxide gas, superimposed upon the deceased's preëxisting heart condition, caused degeneration of the

[24] Taylor, H. F.: The value of electrocardiography in medical underwriting, Proc. Assoc. Life Insur. Med. Dir. America, 1932, xviii, 165–201; Wilson, F. N.: Recent progress in electrocardiography and the interpretation of borderline electrocardiograms, Proc. Assoc. Life Insur. Med. Dir. America, 1938, xxiv, 96–156.

[25] *Carbon Monoxide Poisoning and Electrocardiographic Evidence.* Carbon monoxide poisoning results in impaired capacity of the corpuscles to transport oxygen, and the heart suffers from anoxemia. If the dosage of carbon monoxide be sufficient, heart damage will result, and this may be more extensive in the presence of a preëxisting endocarditis, so as to warrant a professional opinion that the latter was substantially aggravated by the accidental poisoning. A number of cases of cardiac damage through carbon monoxide poisoning have been arising in the workmen's compensation field, and papers have been written devoted to specialized aspects of the electrocardiographic configurations one may expect to find.

deceased's heart muscles and in turn deceased's death from endocarditis. . . ." A very strong contention was made that no definite date of an "accident" had been proved, and that any effects of the carbon monoxide were at most transient and did not accelerate the endocarditis. By a 3–2 decision, the New York Appellate Division affirmed the award.

Reichard v. Franklin Manufacturing Co., 223 App.Div. 797, 228 N.Y.S. 17 (1928), affirmed without opinion in 249 N.Y. 525, 164 N.E. 570.

Comment: The electrocardiogram would give no direct evidence of the presence of endocarditis. The presence of carbon monoxide poisoning of the heart muscle would be shown objectively by the presence of progressive or permanent changes (especially in the RS–T segment and T-waves) similar to that seen in myocardial infarction.[26]

The electrocardiogram, therefore, if taken at the proper time, should provide objective evidence of carbon monoxide poisoning. The Reichard case is one of those where lack of a specific incident and long lapse of time between stimulus and final injury cause natural doubts to arise about causal connections. Electrocardiographic tracings made at once after the initial collapse and at intervals thereafter might well throw valuable light on the cause-effect relationships.

Group IV: Injuries ascribed to psychosomatic stimuli, consisting of nervous shock without substantial impact, or other psychic factors.

The stimulus would need to represent something more than the usual tensions of that type of employment to satisfy the legal definition of an "accident."

Case 5: *Workmen's compensation: Death attributed to acute dilation of heart from shock, excitement and overstrain caused by accidental breaking of steam pipe on crane operated by workman.*

Employee, X, a workman with preëxisting heart disease, was operator of a revolving steam crane mounted on a flat car and used for handling logs. A steam pipe which projected over the end broke. "A dense cloud of escaping steam immediately enveloped the decedent, who was in the cab. The boiler was carrying a capacity load of steam, and, fearful of an explosion, he attempted to pull the fire from under it. He had a weak heart, and it is claimed that because of the shock and excitement, due to the sudden escape of the steam and the fear of the explosion, he became physically unable to put out the fire. He called a fellow workman to assist him, then got out of the cab, and sat down on a log apparently much exhausted. In a few minutes he got into his automobile and drove home. After dinner he rested awhile before driving back to the place where he was employed. He remained there for a few minutes, then returned to his home. Arriving there he rested in bed for two hours. After he arose, he attempted to do some work in mending a chair, but complained of feeling 'done for.' A few minutes later he dropped dead. This was about 4 o'clock in the afternoon. The accident happened at 11:30 a.m. A claim for compensation was made. The defendant denied liability on the ground that there was no accident and no injury and no causal connection whatever between decedent's death and his employment. On the hearing, the commission decided against this contention and filed an award for compensation in the sum of $14 per week for 300 weeks."

[26] Stearns, W. H., Drinker, C. K., and Shaughnessy, T. J.: Changes found in 22 cases of carbon monoxide poisoning, Am. Heart Jr., 1938, xv, 434–447.

No postmortem examination was made. X's family physician gave it as his opinion that "The probability is that the final cause was acute dilation of the heart brought on by overstress and overstrain and excitement."

Held, on appeal: Award affirmed. The court stressed the shortness of the time interval separating stimulus and death, and the fact that X was constantly sick during that period. "The fact that he [X] had a previous disease of the heart, which may also have contributed to his death, is immaterial. The shock and excitement were concurring causes. It is not necessary that they should have been the sole, proximate cause."

Monk v. Charcoal Iron Co., 246 Mich. 193, 224 N.W. 354 (1929).

Case 6: *Tort case: Wrongful death action on behalf of guest against driver for negligently causing automobile accident which allegedly caused guest nervous shock and resultant heart failure.*

B, a 28 year old girl, was riding in the car of C when the latter negligently ran off the traveled highway and tipped over. B suffered various injuries, including nervous shock. Seventeen days later she died of "heart failure." Her administrator sued C for wrongfully causing her death. All admitted that B had suffered from pre-existing heart disease, and defendant C maintained that her death was due solely to it and not to the accident. Plaintiff's doctors testified that the nervous shock of the accident aggravated her heart condition and led to her death. No electrocardiograms were offered in evidence. Verdict and judgment in favor of B's administrator for $2,800 was upheld on appeal.

Albrecht v. Potthoff, 192 Minn. 557, 257 N.W. 377 (1934).

Comment: Obviously it is difficult to establish a cause and effect relationship in such cases. The physiological mechanisms involved are many and will differ depending on the factors and the preëxisting cardiac damage involved in each case. In some instances, however, electrocardiograms may show definite progression of disease or new pathologic lesions following the emotional strain.

At present, the best authenticated type of cardiac disaster due to psychosomatic stimuli is an attack of angina pectoris precipitated by a sudden excess of emotion in one already subject to that disease. Provident and habitual taking of electrocardiographic tracings in cases of collapse following emotional stimuli may help elucidate any cause-effect relationships in respect to other cardiac conditions.

Group V: Miscellaneous medico-legal uses of the electrocardiogram.

A. The Electrocardiogram for Identification Purposes

Sir Thomas Lewis first pointed out identifying properties of electrocardiograms. He said: "The similarity between the electrocardiograms taken from the same subject on different days is so close, and the variations from subject to subject are so numerous (for it may be said that no two series of curves are ever identical), that a series of three leads from any subject would be sufficient to identify the subject in question amongst a considerable number of his fellows." [27]

[27] Lewis, T., and Gilder, M. D. D.: The human electrocardiogram: A preliminary investigation of young male adults, to form a basis for pathological study, Philos. Trans. Roy. Soc. London, Series B, 1912, ccii, 351–376. See also Castellanos, I.: Personal identification by electrocardiography, Jr. Crim. Law and Criminol., 1932, xxiii, 356–360.

Any practical use of the electrocardiogram for identification purposes has been limited by obvious deterrents. It calls for special apparatus, for a technical procedure, and for a skilled interpreter, and further difficulties are introduced by the fact that minor variations do occur in individual patterns from various causes, as we now know. The method would be expensive in money and time as compared with other available means of identification. Furthermore, it would not be useful unless earlier comparison electrocardiograms were on file, an ideal which has not even been attained in the easily executed practice of identification by finger printing. Again, the electrocardiogram could not be used after death of the subject, and the intervention of any cardiac disease in the course of years would radically alter the electrocardiographic configurations.

The identifying properties of the electrocardiogram may assume importance, however, in individual litigation. In the notorious New York conspiracy scheme for simulating heart disease in order to collect insurance disability benefits, X, an insured person, proffered to the insurance company abnormal electrocardiographic tracings allegedly made when he was in hospital on a given date. Careful investigation showed that the tracings were not made at that time, but were made privately a month later, probably after the subject had been digitalized to distort his electrocardiographic tracings. This fact was established by the seizure of other like tracings found in the office of the incriminated doctor. The configurations of the tracings were so near to identical that no doubt existed regarding the certainty of proof. If it should be doubted that the electrocardiograms offered in court were taken from the plaintiff or claimant, there is no reason in most states why the court could not appoint an impartial physician to make new tracings. Usually these would show enough points of similarity or dissimilarity to settle the question of suspected substitution of electrocardiograms.

B. Preëxisting Electrocardiograms as Evidence of Preëxisting Cardiac Disease.

If a person seeking insurance fraudulently conceals preëxisting disease which is material to the risk, courts will permit the insurance company to tender back premiums and obtain cancellation of the policy on the ground of material breach of warranty or fraud. If the assured, in applying for a policy, allegedly suppressed any information regarding prior heart disease, discovery of the fact that previously he had been the subject of electrocardiographic studies would be a most important circumstance going to show guilty knowledge. This is because, at the present time at any rate, it is not a universal custom to make routine electrocardiograms of patients. Some clinicians include this as a part of a routine physical examination of middle aged or elderly individuals, but in the hands of the general practitioner, it is usually a diagnostic refinement utilized only when good grounds exist for suspecting disorder or disease of the heart. It would be open to the assured to dispel inferences of guilty knowledge by producing the electrocardiograms and

showing them to be normal, or to otherwise prove that facts of his heart disease were not communicated or known to him.

Conclusion

We have endeavored in this paper to show what are the main sources of cardiac litigation, to point out basic legal principles important to the problem of proof and to analyze type cases where electrocardiography might be used in court. In doing this we have sought to stress important positive uses of the electrocardiogram while at the same time pointing out great variations in the probative value of this new species of evidence depending on the individual cardiac condition involved. We have stressed, as others have done, the interdependence of electrocardiographic interpretation on sound clinical examination and judgment. It is necessary to shatter any illusions that the electrocardiogram has universal diagnostic authority. It is only by recognizing the critical limitations of a new species of evidence that courts may protect against abuse and injustice likely to arise from extravagant claims regarding its virtue as proof.

PROCEEDINGS OF AMERICAN RHEUMATISM ASSOCIATION, ATLANTIC CITY, JUNE 8, 1942 *

ABSTRACTS AND DISCUSSIONS OF PAPERS

EPIDEMIC RHEUMATIC FEVER †

By PAUL L. BOISVERT, M.D., *New Haven, Connecticut,* M. HENRY DAWSON, M.D., *New York;* FRANCIS F. SCHWENTKER, M.D., *New York,* and JAMES D. TRASK,‡ M.D., *New Haven, Connecticut*

EPIDEMIC rheumatic fever is not a new disease but it does have especial importance in times, such as these, when large numbers of men are concentrated in military cantonments. The term, epidemic rheumatic fever, apparently implies more than is intended. It is used to indicate the presence of a significant number of cases under, as you might say, one roof. If rheumatic fever were a reportable disease in civilian life, it might be found that there would be considerable variations in its incidence from year to year.

Rheumatic fever is an important military disease and its presence offers a new approach to the study of the factors concerned with its production. Data from such studies carried out in Army Camps indicate that there is a strong association between hemolytic streptococcal infections and rheumatic fever. It seems impossible to distinguish between studies on rheumatic fever and those on the control of streptococcal disease in general.

We are much impressed with the care which the rheumatic fever patients receive in the Army Hospitals. Care, according to present-day standards, is excellent.

AN EPIDEMIC OF HEMOLYTIC STREPTOCOCCUS INFECTION AND RHEUMATIC FEVER AMONG NAVAL TRAINEES

By CAPT. R. M. LHAMON, (M.C.) U.S.N., LT. R. H. HUNTINGTON, (M.C.) U.S.N.R., STAFFORD M. WHEELER, M.D., and T. DUCKETT JONES, M.D., *Boston, Massachusetts*

Publication of this paper was withheld.

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Discussion on paper of Dr. Boisvert, et al., "Epidemic Rheumatic Fever," and Capt. Lhamon, et al., "An Epidemic of Hemolytic Streptococcus Infection and Rheumatic Fever among Naval Trainees."

Dr. J. R. Paul, New Haven, Connecticut: It seems to me that the importance of these studies can hardly be overestimated, particularly at this time. They represent the first military epidemics of rheumatic fever that have been observed and studied in this country. That similar situations have existed for many years is evident from the literature from European sources. In past years the British, Italian, French, and German medical literature record so-called epidemics of rheumatic fever among troops, although few analyses were made of these situations. The point was that they exist. That they cannot only occur here, but that they can be extensive, seems evident from this paper, in which an epidemic of 145 cases is described among three others. That they can be studied is obvious and one cannot help feeling that such studies will eventually tell us more about the nature of rheumatic fever, for this problem is now subject to attack from the epidemiological point of view. The first problem is whether the epidemiology of hemolytic streptococcal infections and rheumatic fever are one and the same. Maybe we have been wasting our time in trying to make two diseases out of one.

The late Dr. Trask always maintained that the secret of rheumatic fever would be found in the study of scarlet fever and its complications, and that prediction is coming to the fore in these papers. Scarlet fever is the most spectacular and important of the streptococcal group because it is more definite; it has a rash and is more easily diagnosed. It is the cornerstone of streptococcal infections, as far as the epidemiologist is concerned. Another point is that although rheumatic fever apparently appears sporadically after German measles and other non-streptococcal infections, no epidemics of rheumatic fever have occurred unless they have been in close association with hemolytic streptococcal epidemics.

Dr. M. J. Shapiro, Minneapolis, Minnesota: These two studies emphasize several important points: namely, that crowding intensifies the severity of an epidemic; that introducing uninfected individuals into an infected environment prolongs such an epidemic. This latter point is important in civil as well as in military life. Frequently when an epidemic of contagious disease occurs in a community, the question of whether or not to close the schools becomes a real issue. The present investigation suggests that the schools should be closed when an epidemic occurs.

These reports again emphasize the probability that the streptococcus is the cause of rheumatic fever. Each speaker seems to be about to state definitely that this has been proved. No such proof, however, is yet available. I agree that the streptococcus has something to do with rheumatic fever, but it cannot yet be proved that the streptococcus is the cause of rheumatic fever.

A point of interest was the statement that of 38 cases of rheumatic fever 31 per cent gave a history of previous rheumatic fever. A number of the patients who developed rheumatic heart disease during this epidemic gave evidence of having had cardiac involvement previously. It is apparent that some of the trainees with rheumatic heart disease were incorrectly diagnosed on their entrance examinations. The incidence of cardiac involvement (64 to 67 per cent) in this group of young men between the ages of 17 to 20 seems unusually high, but when it is noted that a considerable number of them had had previous rheumatic infection, the rate does not appear unreasonable.

Dr. A. S. Gordon, Brooklyn, N. Y.: I would like to ask Dr. Jones whether, in view of the present investigation, he would be brave enough to put himself on record as to the etiologic relationship between the streptococcus and rheumatic infections generally, and rheumatic fever in particular.

DR. MAY G. WILSON, New York City: There is another factor to be considered in the epidemiology of rheumatic fever. As Dr. Boisvert has said, since rheumatic fever is not a reportable disease we have no knowledge of fluctuations in incidence in the civilian population. It happens that we have had 105 rheumatic families under observation over a period of 20 years. We were interested in learning whether there was a rise or fall in the prevalence of rheumatic fever. The analysis showed that there was no excess of cases over the number expected on an age and genetic basis for any calendar year over the 20 year period. There was no evidence of a cyclic change or epidemic phase. I think that if Dr. Boisvert would subject his data to further mathematical analysis he might be able to account for the low incidence he observed in the third camp. One can speculate that the prevalence of rheumatic fever is 1, 2 or 3 per cent, and that of these perhaps only 25 per cent did not have heart disease or had it to such a degree that it was not recognized when they were inducted. In this way, a rough estimate might be obtained and he might find that he had just as many as would be expected in the last camp. In our analyses recurrences were not studied, only onsets of the disease.

DR. PHILIP S. HENCH, Rochester, Minnesota: As a rule, those physicians who write about rheumatic fever are not particularly interested in the chronic arthritides, and those who study the latter diseases do not concern themselves especially with rheumatic fever. It would appear as if we had specialists in acute rheumatism distinct from specialists in chronic rheumatism. This separation of interests is unfortunate, for more comparative studies of both acute and chronic cases would doubtless uncover information of much value.

About three weeks ago I had the opportunity of visiting a mid-western naval station where I saw in one day about 110 young sailors with acute rheumatic fever. This single group of 110 youngsters, age 19 to 25 years, each with acute or recurrent rheumatic fever, represented an economic loss to the country of perhaps one or two million dollars in disability pensions and lost salaries and services for the present and future. Unfortunately, the medical authorities in charge were greatly handicapped and limited in what they could do to prevent a further spread of the condition, and laboratory facilities were not adequate enough to permit the institution of any extensive research studies on those already sick with rheumatic fever and on contacts or possible susceptibles. When such outbreaks occur in an army or naval station, what can the medical officer do to restrict its spread, or what can be done in a prophylactic way? I should like to ask Drs. Jones, Paul, and Boisvert for their comments on what those of us who are about to enter military service should do and what chance there is for such military stations to obtain the help of one of the research teams sponsored by the National Research Council.

DR. JACOB S. KOMINZ, Rochester, N. Y.: I have been in practice long enough to observe one factor of this disease. When I started to practice acute rheumatic fever was very common. I found it in stove heated homes. Since improvement in living conditions among families I find acute rheumatic fever is on the downgrade. I find it still in the home where they use an open stove. I wonder whether that plays a part in the barracks which I understand are heated by open stoves. I would like to ask whether there is any connection between rheumatic fever and that type of heating?

DR. ANN G. KUTTNER, Irvington, N. Y.: We have been studying rheumatic fever in a convalescent home for rheumatic children during the past five years. No rheumatic relapses were observed following the "common" cold, epidemic influenza or chickenpox.

During the first year, 1937–1938, 12 of the 108 children in the institution developed pharyngitis due to a Group A hemolytic streptococcus of a single type. Following a latent period six of these 12 children developed rheumatic manifestations.

The following winter, 1938–1939, a larger outbreak of streptococcal pharyngitis occurred during which 32 children developed upper respiratory infections associated with a single type of streptococcus, type 4. Although these cases of pharyngitis were more severe than those observed during the previous winter, not a single child developed rheumatic sequelae. During the winter of 1939–1940 a third outbreak of streptococcal pharyngitis was observed, this time due to Group A streptococcus, type 27. Of the 39 children who developed this infection, eight developed rheumatic recurrences.

Although no rheumatic recurrences were observed in children who escaped streptococcal pharyngitis, not every child who had this type of infection developed rheumatic manifestations and the total number of rheumatic recurrences occurring in the three year period was small. It seemed possible, therefore, that the relationship of the streptococcal pharyngitis to the reactivation of the rheumatic process might have been accidental. To rule out this possibility it was essential to study the effect of preventing streptococcal upper respiratory infections by some means which had no immediate influence on the rheumatic process itself. For this purpose sulfanilamide was chosen, since most observers agree that this drug not only fails to benefit patients with active rheumatic fever, but actually tends to increase the severity of the rheumatic symptoms.

During two successive winters, 1940–1941 and 1941–1942, the 108 children were divided into two groups, matched as closely as possible in regard to age, number of previous rheumatic attacks, and cardiac findings. Beginning in October and continuing until June, half the children were given prophylactic doses of sulfanilamide. The other 54 children served as controls.

During the winter of 1940–1941 thirty cases of streptococcal pharyngitis occurred among the 54 children in the control group. Fourteen of these 30 patients developed rheumatic relapses. During the winter of 1941–1942, 18 children in the control group of 50 developed streptococcal pharyngitis and nine of these showed rheumatic sequelae.

Among the children receiving sulfanilamide during the two winters, only two children developed streptococcal pharyngitis and only one of them showed mild rheumatic manifestations.

The studies, aside from showing the prophylactic value of sulfanilamide in preventing rheumatic relapses, indicate that the relationship between streptococcal pharyngitis and the reactivation of the rheumatic process is specific and establish the importance of Group A hemolytic streptococci as a factor in the etiology of rheumatic fever.

Lieut. Commander LeMoyne C. Kelly (M.C.) V–(S), U. S. N. R., Portsmouth, Virginia: A great many of our patients at the Norfolk Naval Hospital have been in the sick bay of a ship for three to four weeks and by the time they reach us are apparently well. There is no objective evidence of disease such as swelling or any laboratory confirmation. I wonder if Dr. Paul and Dr. Jones would give us the benefit of their advice as to how long we should keep such patients on strict bed rest, because it is often quite a problem. The ships' officers are naturally anxious to have their men returned to duty and the Ward medical officer is the one who has to decide when that can be done with safety.

Dr. M. Henry Dawson, New York City: Epidemics of rheumatic fever occurring among soldiers or sailors in training camps obviously differ in many respects from epidemics of the disease observed in institutions designed for the care of rheumatic subjects. In the latter case presumably every patient is at least potentially susceptible, and the incidence of rheumatic recurrences following hemolytic streptococcal infection will be relatively high. In the former case relatively few will be susceptible and the attack rate will be relatively low, no matter how widespread the

epidemic of hemolytic streptococcal infection may be. It is precisely because of this fact, however, that a study of the type of epidemic seen in the armed forces should yield particularly interesting information.

Epidemics of rheumatic fever are apparently prone to occur among young recruits, particularly among those undergoing intensive training in concentrated areas. A rapid change in personnel with the constant addition of fresh batches of recruits at periodic intervals seems to favor epidemic conditions. The two speakers unfortunately did not have time to refer to two very interesting papers on epidemic rheumatic fever recently published in England. In the first of these Green showed that among the trainees studied the only infection which led to the appearance of rheumatic fever was hemolytic streptococcal infection. He furthermore stressed the importance of a rising population in the maintenance of the epidemic. The second study by Thompson and Glazebrook (1941) was a detailed report on an epidemic of hemolytic streptococcal infection which persisted for 15 months among 2,095 trainees. The average population was some 1,200 and in all there occurred 1,903 cases of tonsillitis. Of these 115 developed clinical rheumatic fever. During the same period 1,243 examples of the common cold were observed but in no instance was this disease followed by rheumatic fever.

COMPARISON OF THE PATHOLOGY OF RHEUMATIC FEVER AND RHEUMATOID ARTHRITIS

By GRANVILLE A. BENNETT, *Boston, Massachusetts*

THE present observations are based on the findings in 150 surgically treated and 48 and 101 autopsied cases of rheumatoid arthritis and rheumatic fever subjects, respectively. This material has been supplemented by numerous biopsy specimens of various lesions, particularly subcutaneous nodules.*

Rheumatic Fever. Some degree of rheumatic carditis was found in all the 101 autopsied cases, and the Aschoff nodule was found in 67 instances. Of the remaining cases, 29 showed myocardial cicatrices, probably healed Aschoff nodules. Eleven patients (nine females and two males) between six and 29 years of age died with bacterial endocarditis and the hearts of four of them showed Aschoff bodies.

Macroscopic changes indicating old or recent pericarditis or both were present in 70. In 33 instances there was either complete or nearly complete obliteration of the pericardial space. Extrapericardial adhesions were found in 40 of the present series.

Although exudative and proliferative changes in the articular tissues of rheumatic fever subjects have been described by others, their incidence in the present series was small. Knee joints known to have been afflicted were examined in 11 of these patients and in four others. Pathological changes were observed in only three instances. In two there was a mild chronic synovitis of non-specific character. The third patient had presented a

* The majority of these cases were studied in the Arthritis Clinic of the Massachusetts General Hospital or at the Rheumatic Clinic of the House of the Good Samaritan by Drs. Walter Bauer and T. Duckett Jones during the past 12 years.

clinical picture that was difficult to distinguish from mild rheumatoid arthritis, and for this reason is described in some detail. She was a woman 45 years of age, who had been told that she had rheumatic fever and rheumatic heart disease five years before her last hospital admission. She had complained periodically of pain and stiffness in most of her joints during the previous five years. On several occasions tenderness, swelling and limitation of motion were elicited in the digital joints. Postmortem examination revealed the typical valvular, myocardial, and pericardial lesions of rheumatic heart disease. Examination of the spine, knees, metatarsophalangeal and interphalangeal joints of the most severely affected toes and the metacarpophalangeal and interphalangeal joints of one affected finger revealed a mild diffuse lymphocytic, plasma cell and mononuclear leukocytic infiltration in the synovial and subsynovial tissues. All other articular structures were negative.

Rheumatoid Arthritis. Postmortem examinations of 48 rheumatoid subjects have revealed that the most constant and significant pathological changes are confined to the skeletal system. Inflammatory lesions characterized by hyperemia and a marked diffuse lymphocytic and plasma cell infiltration of the subsynovial tissues, frequently accompanied by the formation of lymphoid follicles, were the earliest alterations noted. The synovial villi were redundant and thickened and occasionally showed areas of "fibrinoid" degeneration. Little or no fibrinous exudate was found on the synovial lining tissue regardless of the duration of the arthritis. As the disease progressed the chronic inflammatory and proliferative changes in the synovial tissues increased, extending from the perichondrial margins on to the articular surfaces. Later the joint cartilages were reduced in thickness, disrupted and finally partially or completely destroyed. Inflammatory changes of a similar type were frequently observed in the tendon sheaths. Bone atrophy was a constant finding. Localized bone destruction in the subchondral cancellous portions or shafts was frequently noted. Such lesions were usually the result of direct extension of inflamed connective tissue through the eroded articular surfaces or ingrowth along blood vessels through the bony cortex near the articular margins. Varying stages of fibrous and bony ankylosis were observed. Involvement of the terminal phalangeal joints was a frequent finding.

The cause of death in these 48 cases was as follows:

Cause of Death	Cases
1. Heart disease	
a. Coronary artery occlusion	5
b. Bacterial endocarditis	2
c. Myocarditis and aortitis (unknown etiology)	3
d. Cardiovascular syphilis	1
2. Pneumonia	8
3. Central nervous system lesions (hemorrhage and softening)	6
4. Malignancy	5
5. Tuberculosis, nephritis, sepsis and gastrointestinal lesions	4 of each
6. Purpura (gold) and embolism	1 of each

The three patients succumbing to heart disease of unknown cause will be described in detail in a subsequent report. In each instance the clinical and pathological findings relating to the articulations were those of rheumatoid arthritis. The exact cause of the cardiac lesions could not be determined. It is hoped that further study of these and similar cases may aid in ascertaining whether the heart changes represent an unusual manifestation of rheumatoid arthritis, are related in some manner to rheumatic fever, or are associated with a coincidental disease.

Subcutaneous Nodules. It is of interest that in both rheumatic fever and rheumatoid arthritis, subcutaneous nodules appear in approximately 20 per cent of the cases. In a previous communication (1940) it was pointed out that the subcutaneous nodules of these two diseases could usually be distinguished from one another. Study of an additional 24 nodules from rheumatoid arthritis patients and 23 from rheumatic fever subjects has further assured us that such differentiation is usually possible. It is believed that among the various tissue changes of rheumatoid arthritis, the subcutaneous nodule, when present, constitutes the most characteristic single lesion.

Conclusion. It is apparent that the usual anatomical changes observed in rheumatoid arthritis differ so markedly from those of rheumatic fever that one must infer that the pathogenesis of the observed lesions is different. Therefore, in the absence of etiological evidence to the contrary it would seem advisable to continue to look upon rheumatic fever and rheumatoid arthritis as separate and distinct entities.

RHEUMATIC HEART DISEASE IN AUTOPSIED CASES OF RHEUMATOID ARTHRITIS

(Abstract)

By THEODORE B. BAYLES, M.D., *Boston, Massachusetts*

OF 23 autopsied cases of rheumatoid arthritis six were found to have changes in both the heart valve leaflets and the myocardium similar to those that usually follow rheumatic fever. The histologic lesions of one of these six could possibly be considered active and five were inactive in character. Excluding one patient because of definite rheumatic fever and rheumatic heart disease in childhood, 22 per cent had rheumatic cardiac lesions. The factors of accentuation on cardiac death, the relatively large group with cardiac changes antemortem as compared to control groups, and the small number of cases (possibly one) with active rheumatic fever lesions have been pointed out. No patient who had histologic evidence of rheumatic fever failed to show evidence of this on gross examination. A coincidence, a relationship between rheumatic fever and rheumatoid arthritis or the possibility that the heart disease is related to rheumatoid arthritis might be

inferred from these data. Since patients with rheumatoid arthritis have to die of some other cause than their disease, we wish, as yet, to delay a final conclusion until further studies teach us which one of the above three situations truly obtains. In the clinical treatment of these patients, we have preferred to consider the cardiac changes a coincidence of rheumatic heart disease and rheumatoid arthritis.

THE CAUSE OF DEATH IN THIRTY CASES OF RHEUMATOID ARTHRITIS

(Abstract)

By Edward F. Rosenberg, *Chicago, Illinois*, Archie H. Baggenstoss, and Philip S. Hench, *Rochester, Minnesota*

We have studied the cause of death in 30 cases of rheumatoid arthritis. This number represents all the cases of this condition in which necropsy has been performed at the Mayo Clinic in the past 25 years.

In each case the arthritis had been progressive and had produced some degree of crippling. The articular changes were easily detected and included spindle shaped swellings of joints, atrophy of muscles, synovial thickening and effusions, and some degree of fibrous ankylosis. In a few early cases roentgenograms were negative, but in most of the cases the roentgenograms showed swellings of soft tissues, osteoporosis, varying degrees of destruction of cartilage and bone, narrowing of joint spaces, and sometimes marginal lipping. Constitutional reactions were commonly present.

A history of rheumatic fever was obtained from only two of the 30 patients. The ages of the patients at time of death ranged from nine to 77 years; the majority were in the third to the sixth decade of life. The series included 17 males and 13 females.

Cardiac lesions indistinguishable from those of rheumatic heart disease were found in 16 cases; seven of these proved fatal. Nonrheumatic heart disease was present in eight cases and proved fatal in two cases. Coronary occlusion caused the death in one of these cases; myocardial degeneration of an unknown cause in the other.

Eleven patients died of pulmonary disease, including bronchiectasis with diffuse pulmonary suppuration, pulmonary embolism, bronchopneumonia, pulmonary fat embolism, and massive collapse of the lungs.

Three patients died of renal disease; two from acute pyelonephritis with anuria and one from severe amyloidosis. Two patients died after long continued diarrhea of an unknown origin.

In five cases deaths resulted from miscellaneous causes including cinchophen hepatitis, accidental violence, carcinoma, sudden death during surgical anesthesia, and in one case the manner of death was unknown.

The causes of death can be classified into three groups. In the first group the fatalities were not in any way related to the arthritis, deaths being due to coronary occlusion, pulmonary suppuration, accidental death and death from carcinoma. In the second group, deaths resulted from some form of therapy undertaken for the arthritis, for example, deaths from reactions to typhoid vaccine, from cinchophen hepatitis, fat embolism following manipulations of joints and pulmonary embolism following applications of casts. In the third group the deaths appear to have resulted from visceral diseases which probably represented a part of the rheumatoid disease, for example, rheumatic heart disease, amyloid degeneration, or prolonged exhausting diarrhea.

Discussion on papers of Dr. Bennett; Dr. Bayles; Dr. Rosenberg et al.

Dr. Currier McEwen, New York City: Dr. Hench has mentioned that our Society tends to be made up of two groups: those interested primarily in chronic arthritis and those concerned with rheumatic fever. Today's program, however, gives striking proof of the value of studying the rheumatic diseases as a whole. I, for one, feel that these three papers which we have just heard on the pathologic changes in the heart in the two diseases have made this one of the most profitable meetings I have attended. My first comment is one of admiration for all of those who have been able to get together so many necropsies on patients with rheumatoid arthritis. From personal experience I know how difficult it is and what a careful follow-up it entails. Dr. Bennett's presentation of the pathologic findings and the slides were a treat for all of us. I would like to ask him whether in the course of his examination of the tissues he came on anything that might throw light on the controversial question of fibrositis? Aside from the changes in tendon sheaths and joints was there inflammation in other supporting fibrous tissue such as tendons or fascia or in the muscles?

There are a good many who believe that rheumatic fever and rheumatoid arthritis are closely related, and the similarity of the subcutaneous nodules occurring in the two diseases is one of the strong arguments usually advanced in favor of that view. Dr. Bennett's pathologic observations cast doubt on the validity of that argument for he finds the nodules different. I am still of the opinion, however, that the differences he has pointed out are explainable on the basis of the differences in age and size of the nodules in rheumatic fever and rheumatoid arthritis.

Dr. M. H. Dawson, New York City: I think the papers which have been presented speak for themselves. What is needed in this study is further information, and such information is gradually being assembled. I would like to ask Dr. Bennett what the underlying lesion was in the three cases of subacute bacterial endocarditis, particularly if there was underlying rheumatic disease. I have always felt that the nodule from a classical case of rheumatoid arthritis was quite different from that seen in a classical case of rheumatic fever. However, I would like to reaffirm my belief that all intermediate stages occur. If one studies nodules which have persisted for many months in rheumatic fever one will find them surprisingly similar to nodules of corresponding duration in rheumatoid arthritis. Conversely, if one studies an early and acute lesion in a fulminating case of rheumatoid arthritis, and such do occasionally occur, one is impressed with the similarity which they show to the nodules of rheumatic fever. Finally in such a comparative study one should be sure that one is comparing tissue from individuals in the same decade of life.

In evaluating the frequency of rheumatic hearts in rheumatoid arthritis, I believe that all the alternatives Dr. Rosenberg spoke of must be considered. In particular, much depends upon the type of material one studies. At the Research Hospital for Chronic Diseases on Welfare Island, Dr. Steiner examined 40 rheumatoid arthritis patients very carefully for evidence of rheumatic heart disease. Thirty-five per cent were found to be so affected. Now I do not suggest that 35 per cent of all patients with rheumatoid arthritis have rheumatic hearts but such was the case in a limited series carefully studied. In a few instances the electrocardiographic changes were minimal and could not have been detected had not frequent tracings been made.

Finally, one cannot refrain from commenting upon the *immediate* cause of death in many of the cases reported here today. One notes deaths attributed to cinchophen, typhoid vaccine, foreign protein therapy, and to manipulations. Such a record is not a happy one, but it will at least serve to remind those who consider gold salts too dangerous that other therapeutic measures are also not without danger in this disease.

Dr. D. M. Angevine, Wilmington, Delaware: I wish to express my admiration of the technical excellence of Dr. Bennett's presentation.

Dr. Bennett mentioned that the presence of clusters of lymphocytes in long standing cases might indicate "activity." Such focal accumulations of lymphocytes are seen fairly frequently in sites such as the renal pelvis, or urinary bladder and although they probably indicate some previous infection one does not usually associate such an observation with active inflammation.

The muscle studies were of considerable interest and it is to be hoped that they will be continued. I am in complete accord with the statement that rheumatoid arthritis and rheumatic fever should be considered as separate entities. I should like to ask Dr. Bennett two questions: (1) Were any pathological changes noted in serous cavities other than those described in the pericardial sac? (2) How frequently was amyloid disease observed in this series of cases?

Dr. Bayles included cases of Strümpell-Marie spondylitis and Still's disease in his series of cases. Although these conditions should rightly be considered as rheumatoid arthritis it would seem best in an anatomical study of this nature to make some separation especially where there are so few cases in the series. It also would be preferable not to mention a "questionable Aschoff body." Many such lesions are confusing but the pathologist should state that in his opinion the lesion is or is not an Aschoff body. Of course there will be a great deal of variation among pathologists.

With the criteria that Dr. Rosenberg has set up for the diagnosis of rheumatic heart disease it is difficult to see how he could avoid making such a diagnosis on any heart. With our present state of knowledge it is difficult to know exactly what significance to attach to calcification of the aortic valve.

Dr. B. Leichtentritt, Eloise, Michigan: The peripheral nerves of eight autopsied cases of typical rheumatoid arthritis were examined by Drs. H. A. Freund, G. Steiner, A. E. Price and myself. In seven cases small nodules were observed in the perineurium. We consider these lesions specific for rheumatoid arthritis and suggest the name rheumarthritic nodulous perineuritis.

The nodules were usually located in the perineurium, and rarely in the epineurium, but never in the endoneurium. When stained with hematoxylin-eosin the nodules are visible to the naked eye as bluish round or oval shaped lesions. The size of a single nodule varied between 0.14 and 0.2 mm. in diameter.

The microscopic appearance was characteristic, showing three different zones: first, a lymphocytic and plasma cell peripheral ring; next, a middle zone of polyhedral cells with large irregular nuclei poor in chromatin, comparable to the epithelioid cells of other granulomatous tissues; and third, an innermost pale and acellular

center with homogenously staining masses in which are occasionally embedded small dark granules of nuclear debris.

There are some variations of the layers: the acellular center may be missing, the inner zone may contain a central blood vessel, or the intermediate zone may be represented only by a few epithelioid cells.

As a control we studied more than 100 cases of various nonarthritic diseases and in no instance were similar lesions found.

Because these lesions were found in seven of the eight cases examined, because of the regularity with which they occur in the perineurium or near the epineurium, and because of their sharply circumscribed nodular character, we believe these lesions of the peripheral nerves are a specific pathological feature of rheumatoid arthritis.

Dr. Hugo A. Freund, Detroit, Michigan: I have been convinced for many years of the likelihood of a nervous system involvement in rheumatoid arthritis. The pain along the course of the nerves, sweating, glossy skin, interosseous muscle atrophy, hyperactive reflexes, and numerous other lesser changes could be explained only on the basis of nerve, ganglion, or spinal cord involvement. Dr. Alvin E. Price and I have studied cases clinically for many years. We have been able, with the assistance of Dr. Bruno Leichtentritt, and Dr. Gabriel Steiner, to show that nodules of specific character are found in the perineurium of the peripheral nerve. Dr. Leichtentritt has just described these nodules. They have not been found in controlled cases, and appear to be specific in rheumatoid or atrophic arthritis. Clinically, these findings explain many of the signs and symptoms of the disease.

Dr. Walter Bauer, Boston, Massachusetts: In reviewing our series, Dr. L. Raymond Morrison found eight cases that showed peripheral nerve changes similar to those described by Dr. Steiner. Other changes were noted in the spinal cord; these will be reported at a later date.

Dr. Charley J. Smyth, Eloise, Michigan: I would like to add a few remarks concerning 10 patients seen at Eloise, Michigan. All were unquestionably cases of rheumatoid arthritis. As far as could be determined 50 per cent had both gross and microscopic lesions of rheumatic heart disease.

With relation to Dr. Leichtentritt's comments regarding the peripheral nerves, in four of the five cases in whom peripheral nerves were studied, findings compatible with rheumatic heart disease were observed. Two of these 10 patients died from myocardial infarction. In no instance was the diagnosis of rheumatic heart disease established during life.

The occurrence of this high percentage of lesions characteristic of rheumatic heart disease is strong evidence to indicate that rheumatoid arthritis and rheumatic fever are related.

Dr. Granville A. Bennett, Boston, Massachusetts (closing): Dr. McEwen has inquired about the pathology of fibrositis. Our material from cases of this disorder is small and I do not feel justified in attempting to interpret such lesions as have been observed.

In reply to the comments of Drs. McEwen and Dawson on the similarity of the subcutaneous nodules of rheumatic fever and rheumatoid arthritis, I wish to acknowledge the general morphological resemblances of these lesions. On morphological grounds, however, taking all cases in our series as they have come, it usually has been possible to distinguish between these particular lesions.

The cases of bacterial endocarditis about which Dr. Dawson inquires are noted on a short table in which the cardiac lesions of the 48 autopsied cases of rheumatoid arthritis have been tabulated. Twenty-four patients showed pathological changes in the heart and pericardium. These lesions were interpreted as follows:

(*a*) Probably rheumatic heart disease—seven cases. In these cases there were valvular lesions that appeared to have resulted from rheumatic endocarditis.
(*b*) Possibly rheumatic heart disease—three cases. (In two of these there were bacterial vegetations upon deformed valves.)
(*c*) Pericarditis or pericardial scarring of unknown etiology—three cases.
(*d*) Carditis and aortitis of unknown etiology—three cases. (A terminal hemolytic streptococcus bacteremia was present in one of these patients.)
(*e*) Heart lesions unrelated to rheumatic fever—eight cases.

No Aschoff nodules were observed in any of these 24 cases.

Dr. Angevine has commented on the lymphocytic infiltration of the synovial tissues. I have considered the presence of such infiltrations to be an indication of continued activity of the rheumatoid arthritis process. Such a cellular response can best be explained as a reaction to some form of local tissue injury. I cannot answer Dr. Angevine's question concerning the frequency with which the various serous cavities have been affected. Eleven of our cases showed amyloid infiltration. Nephritis was present in seven instances. Of these there were four cases classified as glomerular nephritis.

Dr. Leichtentritt's findings with regard to peripheral nerve lesions in patients with rheumatoid arthritis promise to be of considerable interest. Our material will be investigated with these observations in mind.

Dr. E. F. Rosenberg, Chicago, Illinois (closing): Dr. Angevine has raised the question as to whether the lesions I have shown in the hearts were really lesions of rheumatic fever. In answer, I wish to say that we have studied them carefully and we are personally convinced that the lesions are indistinguishable from the lesions of classic rheumatic heart disease. Furthermore, we have not been satisfied to rely on our own impressions concerning this important point, and, therefore, submitted the specimens to Dr. H. E. Robertson of the Department of Pathology of the Mayo Clinic, and also to Dr. B. J. Clawson, of the Department of Pathology of the University of Minnesota. Both of these experienced pathologists have agreed independently that the specimens do show the lesions of rheumatic heart disease.

THE PRESIDENT'S ADDRESS

Loring T. Swaim, M.D., *Boston, Massachusetts*

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The conditions of total war have no precedent. The medical profession has responded magnificently with bold and novel remedies until recently unheard of. Total war is also waged against the courage and spirit of man. Therefore, a new morale is demanded as an important factor for victory.

The medical profession is always pioneering into the unknown fearlessly and unselfishly. Doctors have the good of the community at heart and the spirit of the Good Samaritan as a way of life, so that the goal I am pointing out for medicine is consistent and logical.

Total victory calls for unheard of human sacrifice. It calls for a supreme state of fitness, physically, mentally and spiritually, the extra plus in

living and in inspired thinking. The medical profession *can* and *must* play a major rôle in the attainment of that total national fitness.

The profession must look to the future. We have an important part in equipping the American people for that great job of reconstruction in the critical post-war years.

Never before have civilians been forced to suffer in the same way as is happening on such a huge scale in the world. The post-war period will bring unique problems of adjustment, one of which will be finding the way to free people from bitterness and hate.

The challenge to medicine is not only to cure the bodies but to find the spiritual answer to these emotions and lay the foundations for curing a diseased and maimed world.

Doctors have pioneered in medicine. Why should we not pioneer into the great intriguing soul in man which is spiritually ill, and heal it? Dr. Steinmetz has predicted that the next important discoveries will be along spiritual lines. America can be the nation, the pioneer, to give that necessary new thinking and living to the world. Because of experiments with arthritic patients I am convinced that these predictions can be realized. A simple plan is suggested by the following experiences.

Rheumatoid arthritis is a constitutional disease. Since the disease affects all parts of the individual, to get the best results we must treat the whole individual, not only his body and mind but his *soul*. We have made great strides in the medical care of rheumatoid arthritis, in diet, rest, gold salts and medicines, and building body resistance. Deformities can be prevented by orthopedic care. Surgery is able to restore deformed joints to comparative usefulness. These are all essential in the treatment. Yet evidence accumulates that physical health is closely related to spiritual health. No constitutional disease is free from the effects of mental states. Rheumatoid arthritis is no exception.

The effect of emotional upsets can no longer be considered mere coincidence. My investigations in the last 10 years show that anxiety and resentment are the two most constant emotional reactions in rheumatoid arthritis, and maladjusted human relationships are a real problem.

Why are resentments and fears the most common reactions? What fault of character has been developed? What quality of heart is lacking? The selfish character is usually fearful, worrying, resentful and easily angered; the unselfish character is loving, fearless, forgiving in its attitude. This is true in my series of 171 cases. The question is how to change individual character so that there is no selfishness. We cannot of ourselves change the quality of our spirit. What we really want is a new spirit in man, new motives of friendship, patriotism and world outlook, a new philosophy for living.

There are spiritual laws which will change lives if they are scientifically applied and a new spirit results. The patients I have studied make me

believe that all forms of selfishness point to a starved, undeveloped spiritual life. The spiritual life needs to be nurtured to develop an unselfish character.

A plan has evolved for feeding a starved spirit. Besides the medical history questions are asked about intimate relationships with members of his family, friends, and in business. It is essential to help people see their own failings of disposition, and rectify their own mistakes. With friendly confidence people instinctively tell the truth about their resentments and fears.

Next explore the personal beliefs or set of standards by which the person actually lives. Find out if his beliefs affect his thinking and actions or are purely intellectual, for on these foundations we must build as stepping stones to further growth. Day by day by explaining and teaching the spiritual laws of the Bible, by times of directed reading and thinking along lines of conduct such as honesty, unselfish living, care for others, the patients grow in understanding. People do not know how to be honest and are blind to their motives.

For example, without any physical reason a woman in the hospital began to vomit every morning after breakfast. She was full of self-pity and resentment against others in her ward who had visitors while she had none. She was blind to her jealousy but when she realized her self-absorption she repented and apologized, and thus restored friendly relations with her neighbors. This cured her resentments and her illness. Her whole life was changed by the application of this simple principle of repentance and apology as an answer to resentments, for her life was a series of resentments at home.

Let me illustrate what happens to character when this sort of spiritual education is carried out. A woman of 32 who had had an unhappy marriage obtained a divorce. Through propinquity and lack of funds she drifted into certain unfortunate relationships, making her dependent and helpless. Her vitality was lowered by constant fear and resentment. Typical rheumatoid arthritis developed. She was unable to walk for six months. Her relationships were all wrong. Her early religious belief was weak and almost gone from neglect. Daily Bible study, reading and thinking were started. Her spiritual life grew. Because of the change in her she found work, married again, and is now doing all her own housework. The most remarkable change has been in her emotional reactions to life which are now outgoing, unselfish and fearless. A new faith, hope and caring for people have completely changed her earlier way of life, have given her courage to face the previous defeats and not succumb, to stand up to those who have tried to pull her back to the old life. She has really found a victorious life. She has an unwavering faith in God and His direction. The old reactions no longer occur. She knows the value of spiritual health and sets aside time for it each day. Her joints improved. Now her arthritis is inactive. I cannot say that she recovered from her arthritis because of the development of her spirit, but it was an essential factor in her final recovery.

A man at the age of 50 came for the treatment of rheumatoid arthritis. His weight was down from 175 to 149 pounds. His relationship history showed a deeply rooted resentment of many years' standing associated with people in his work and his home relationships were strained. Although entirely successful in business he had a sense of complete failure about his whole life. He had only an inherited belief which was undeveloped and superficial, in no way affecting his thinking or life.

He faced facts and made a new start. He began spiritual training. During the first year there was a complete change in this man's physical health. He gained 30 pounds. The rheumatoid condition cleared up. His emotional outlook has changed, old resentments have been cleared up by apology; the whole family relationship is different. In the last nine years his spiritual foundations have been so firmly laid that they are the basis for his conduct. A new spirit has come in his job and he is helping many of his associates, for when people find this new experience the best way to keep it fresh and vital is to help others.

There are many patients who came for arthritis and really were spiritually starved and who through feeding their spiritual lives have found that their whole personalities were changed. There is very little conception of these great spiritual forces. People do grow and their lives deepen as they develop a personal relationship with God. This superforce is the crux of the change.

The spiritual approach does not cure the arthritis, but it is an essential factor, a factor without which the patient cannot advance beyond a certain point. It has a very definite place in "complete treatment." It makes people live victoriously. If "complete treatment" could be instituted early there would be very many fewer cripples, and if people would cultivate a mature, developed faith and belief in a superforce as part of their character they would never react with fear and anger the way they do under emotional strain. This "complete treatment" is no longer an experiment with me, but medical success or failure in many cases depends on this spiritual factor.

Consider the situation of our nation, and our responsibility for building the future world order. The world is sick today because nations have been starved exactly the way these patients have been starved. The nations have not learned to live together any more harmoniously than these patients have. The remedy is the same, i.e., to feed the spiritual lives of nations through individuals. The world to be must have this new spirit. In the passing world selfishness prevails. If this quality is carried over, the world will be actually in essence the same. A new order requires a new spirit.

Doctors are admittedly leaders. Shall we pioneer again and seek this new spirit for ourselves that we may guide our nation and the world to the highest spiritually? "The trouble with nations is human relations, especially you and me." A determined minority could remake the world. Shall we lead the way to bring about the greatest revolution in all time, the revolution in the hearts of men?

FOOD ALLERGY AS A POSSIBLE FACTOR IN SUBACUTE RECURRENT ARTHRITIS

(Abstract)

By WARREN T. VAUGHAN, M.D., *Richmond, Virginia*

IN a consecutive series of 1000 adults complaining primarily of allergy (asthma, hay fever, urticaria, migraine and allergic dermatitis and indigestion), 27 had recurrent subacute involvement of various joints. The allergic etiology in these 27 cases was indicated either by the fact that the causative foods were discovered and the attacks prevented by their avoidance, or that, although the etiologic foods were not discovered, the joint manifestations appeared synchronously with other allergic symptoms and were relieved with improvement in the latter.

Thirty-two foods were incriminated. Strawberry and tomato, the "hearsay" foods customarily suspected in rheumatism, were relatively unimportant in this list.

Four had intermittent hydroarthrosis. One had intermittent hydroarthrosis superimposed on chronic rheumatoid arthritis. Thirteen showed predilection to involvement of the small joints with symptoms resembling rheumatoid arthritis. In some, the joint symptoms were intermittent, in others, they were chronic with exacerbations. In the former one must consider a condition similar to intermittent hydroarthrosis with predilection for small joints, whereas in the latter one must consider true chronic arthritis with exacerbations caused by allergenic foods. Those with negative physical findings at the time of examination may belong in the group with intermittent hydroarthrosis of large or small joints. Detailed illustrative case histories are given.

This series is compared with Kahlmeter's 54 cases attributed to allergy, among approximately 5,000 rheumatics; Solis-Cohen's 27 cases observed in 20 years in whom allergy may have played a part, and Hench and Rosenberg's 34 cases of recurrent or palindromic rheumatism.

In the author's series all patients were allergic to foods, although in two instances inhalant allergens appeared to play exciting rôles.

Although food allergy has not been proved to play a part in the majority of arthritics, there appears to be a small group in whom intermittent hydroarthrosis involving large joints or multiple small joints (with a picture of recurrent subacute rheumatoid arthritis) may be caused by food allergens. This may occur in persons whose joints are normal between attacks or may appear as an exacerbation in persons with chronic arthritis, presumably not caused by food allergy. It may occur in osteoarthritis, rheumatoid arthritis, or combined arthritis, but in all cases, when small joints are involved, the picture is "rheumatoid."

Discussion on paper of Dr. Vaughan, "Food Allergy as a Possible Factor in Subacute Recurrent Arthritis"

DR. RALPH PEMBERTON, Philadelphia, Pennsylvania: This paper by Dr. Vaughan is timely. Fifteen years ago Dr. Harry Wilmer studied with me a series of cases at the Presbyterian Hospital in Philadelphia but our results were negative. About eight years ago another series of cases was studied with Dr. Wilmer and Dr. Merle Miller but the results were again negative. The positive results reported by Dr. Vaughan, however, may have more significance. About eight years ago there appeared a paper from the Central Institute of Public Nutrition in Moscow by Pevsner et al. in which these authors reported a series of cases which they believed to have been benefited by restrictions of diet. They related this benefit to a form of desensitization.

Many of us have been increasingly impressed by the value of rest and sedation of the nervous system in the treatment of arthritis. Allergic reactions involve the nervous system and it is possible that some of the benefit in the favorable cases reported derive in part from this premise. Only recently two physicians whose symptoms cleared up satisfactorily on the basis of rest and mild sedation, told me that they would not have believed without experience that their arthritic symptoms could be made to subside so easily. There is obviously a need for further observation of these angles of the arthritic problem and I hope that Dr. Vaughan will continue his studies.

DR. RUSSELL L. CECIL, New York City: I am very glad Dr. Vaughan has made this study and I hope he will continue it, because it is along a line that has been rather neglected in the study of arthritis. We are all familiar with the studies made by Swift and Klinge, both of whom pointed out certain similarities between the lesions of rheumatic fever and arthritis and those of hyperergy both in human and animal experiments. Dr. Swift noted a similarity between joint lesions in serum sickness and rheumatic fever. When you think about it, it is surprising that we do not see reactions of hyperergy more often in joints than we do. Klinge's experiments always interested me, namely, hyperergy produced in the joints of animals by the injection of serum or albumin. If arthritis is an expression of an allergic state in the joint no one has yet indicated what form of allergy it is. As Dr. Vaughan suggests, it is probably not an inhalant, possibly a food, possibly bacteria.

A few years ago Dr. Wainwright gave an interesting report before this Society on streptococcal skin tests and used streptococci which had been recovered from patients with rheumatoid arthritis for vaccine therapy. The criticism made at that time has been heard since, namely, that so many normal individuals have positive skin reactions to streptococci and other bacteria that positive reactions in an arthritis have very little significance. When we come to consider the different forms of arthritis in relation to allergy, the problem is even more difficult. We have patients who tell us they have pains in their joints and that after eating certain foods, the pain is increased. However, in going back over my personal experience, I have great difficulty in recalling any case in which there was actually a connection between food and swelling. I recall a case years ago of a young women who came to the Cornell Clinic with typical rheumatoid arthritis. She felt that food had something to do with it. We tried putting her on a fast for a week, with nothing but water and weak tea. She stuck to the fast very faithfully. She came in at the end of the week with a remarkable improvement. She went into a typical remission, and gradually went back to her original diet. The unfortunate part of the story was that later on she had a recurrence and when the fast was repeated no benefit was obtained.

As far as hypertrophic arthritis is concerned, I cannot feel that allergy has anything to do with it. Pemberton made studies on carbohydrate metabolism in patients with osteoarthritis and felt that these patients were helped by a low carbohydrate diet. Acute gout is often claimed to be a form of allergy, but that has to be proved. It

seems to me we make a mistake in placing too much emphasis on what patients state. We all get joint pains, not so much from food as from alcohol in various forms. Certainly some of the heavy wines are conducive to a feeling of stiffness which could not be called gout but possibly a fibrositic form of rheumatism. We have to bear in mind that allergy and arthritis are both common; some forms of allergy are extremely common and we have to allow for a certain amount of coincidence in these two conditions.

I cannot say very much about palindromic arthritis though it certainly bears some resemblance to an allergic condition. I would like to ask Dr. Vaughan to say a word more about the second case in the series of patients he described.

Dr. Francis C. Hall, Boston, Massachusetts: We have been interested for 20 years in the possibility that food allergy is a factor in arthritis. Dr. George Minot raised this question about that time, pointing out that there was some evidence suggesting that people with arthritis were particularly subject to allergies of various kinds, and had family histories of allergy. Therefore, we have had allergy in mind over the years, and have looked into the matter when taking histories.

We have not found food allergies common in people complaining of joint disturbances. Every once in a while one sees a person who has skin allergy, or asthma, and swelling of the joints associated with the eating of some food. Usually the patient has determined this relationship, however, and these joint swellings are of a very transient nature if the patient omits the offending food.

One of our leading allergists in Boston, Dr. Francis Rackemann, has made the statement that of all the patients that he sees come into his office with various types of allergy, patients with arthritis are conspicuously absent. We have rarely found allergy present in patients with either of the two main types of chronic arthritis, though in addition to looking for it in the record, we have intermittently done skin tests.

Dr. A. S. Gordon, Brooklyn, N. Y.: I would like to ask Dr. Vaughan in reference to his group of cases, what were the eosinophile counts, and the sedimentation rates; and did he succeed in obtaining passive transfers in these cases?

Dr. Warren T. Vaughan, Richmond, Virginia: Several years ago a patient said that strawberries and tomatoes caused her rheumatism. Doctors are as much at fault as the laity in suggesting that strawberries and tomatoes cause rheumatism. To our surprise we found that she was allergic to these two foods. She improved on avoidance. Then we started testing all rheumatics with foods but gave up after 25 patients, because we were getting nowhere. My interest was drawn back to this recently in this series of patients with the picture of intermittent arthritis involving small joints. I found cases in which non-allergic chronic rheumatic involvement was accentuated by food allergens. I would emphasize the infrequency of the condition rather than its frequency.

We do know that joint involvement may be a part of an allergic reaction as we see it in serum disease.

As far as the eosinophile count, sedimentation rate and passive transfer are concerned, I cannot give you any information from my studies. Studies of passive transfer and eosinophila would be of little benefit since they are notoriously inconstant in food allergy, but the sedimentation rate might enable us to discriminate between allergic reactions and exacerbations due to infection.

RHEUMATOID SPONDYLITIS AS A CAUSE OF INCREASED CEREBROSPINAL FLUID PROTEIN. BASED ON THE STUDY OF 101 PATIENTS WITH RHEUMATOID ARTHRITIS

By Alfred O. Ludwig, M.D., Charles L. Short, M.D., and Walter Bauer, M.D., *Boston, Massachusetts*

The neurologic manifestations of rheumatoid arthritis are numerous, extremely variable and at times so striking as to simulate disease of the central or peripheral nervous system. An analysis of these clinical features in 293 unselected consecutive patients with rheumatoid arthritis and the results of detailed neuropathological studies are in progress. The present report deals only with the cerebrospinal fluid findings in this disease.

The cerebrospinal fluids examined during the course of this study were obtained from 101 patients with rheumatoid arthritis, 59 of whom suffered from peripheral joint disease alone and 42 from spondylitis with or without peripheral joint involvement. Cerebrospinal fluid analyses were repeated in 11 instances (seven patients with and four without spondylitis).

The only significant abnormalities observed were increased total protein, abnormal colloidal gold curves or a combination of the two. The fact that 15 of the 16 patients with increased spinal fluid protein had either spondylitis or symptoms suggesting spinal involvement strongly suggests a relationship between an elevation of the spinal fluid protein and the presence of rheumatoid arthritis in the spinal and sacroiliac articulations. Such alterations occurred more frequently in the spondylitis patients with severe pain or sciatica or both and hence presumably a higher degree of inflammatory activity. Factors probably involved in the production of these abnormalities are alterations in the serum proteins and increased permeability of the meninges because of their proximity to the inflamed articular tissue.

TREATMENT OF TWO HUNDRED CASES OF CHRONIC ARTHRITIS WITH MASSIVE DOSES OF VITAMIN D PREPARED BY THE WHITTIER METHOD

By R. Garfield Snyder, M.D., Willard Haywood Squires, M.D., John Wilfrid Forster, M.D., and Cornelius Horace Traeger, M.D., *New York, N. Y.*

This study was to determine (1) the toxicity and (2) the therapeutic value of treatment with massive doses of vitamin D. The dosage used varied from 100,000 to 500,000 units daily. The average dose was 200,000 to 300,000 units. Within the limits of this dosage, in over five years, no deaths occurred and no evidence of serious toxicity was observed. No definite increase in the calcification of the blood vessels, as proved by roent-

genograms, occurred, nor were there any evidences of stone formations in the kidney or gall-bladder or recalcification of bones. A few cases developed mild toxic symptoms such as nausea with occasional vomiting, but they were easily controlled by stopping the medication for a few days. In a few cases moderate hypercalcemia was noted, but was easily controlled by reduction or complete cessation of the medication for a few days.

The authors presented a moving picture of five patients before, during and one year subsequent to the institution of treatment.

The results in the last series of 50 cases were as follows: 7—excellent, 20—good, 8—fair, 9—slight improvement, and 6—failures. The percentage of excellent results is not high, but the cases were especially selected as a severe test for this new method of treatment. With rare exception, all were of over two years' duration, and more than half had had arthritis for some five to 25 years. The few patients selected who had had the disease for less than two years were chosen solely because the rapid downward progress of the disease made them a severe test for any form of treatment. To eliminate the possibility of spontaneous exacerbations and remissions, the great majority of the patients in this series had been under observation for at least two years and had previously proved resistant to all tried forms of therapy.

Because there is no specific for chronic arthritis, any new form of treatment which promises a fair chance for improving a refractory case should be welcomed as an additional form of therapy, especially as it has been found that this medication is not harmful in the dosages employed. It apparently is not a specific, and it is not known how it acts, but this is equally true of the sulfonamides, salvarsan, gold, etc. Obviously it is a powerful tonic as the patients usually gain weight and feel better. It is believed that the improvement observed was not coincidental to the "burning out of the disease." It would be most improbable that such improvement would occur suddenly from natural causes. It should also be noted that following the cessation of treatment, the improvement was sustained for weeks and even months in a large percentage of cases.

EVALUATION OF ARTHRITIC CASES TREATED BY VITAMIN D

By Lewis Clark Wagner, M.D., *New York City*

When the research work on chronic arthritis was begun at the Hospital for Ruptured and Crippled with vitamin D therapy, it was considered best to have an impartial orthopedic surgeon evaluate the results of the cases under treatment. He was to have nothing to do with the general care and treatment of the patients, but examined each patient on his first visit to the clinic and reëxamined him at the end of one year.

These patients were examined very thoroughly, the examinations involving all the locomotive systems of the body. In general, each examination included the appearance of the patient and described his habitus, his method of walking if possible, and his activities. The loss or gain of weight was noted, as was the patient's normal size. All joints were tested as to range of motion and the major joints were measured. Deformities and swellings of the joints were tabulated. Muscle strengths were estimated and disabilities noted.

At the end of one year, these patients were seen again, and a separate, thorough examination was made. By comparing the two examinations, one was able to deduce whether there had been any improvement or not.

In the final evaluation of these cases it was necessary to have certain criteria from which to arrive at one's conclusions. These were as follows: (1) feels better; (2) increased weight; (3) loss of pain; (4) increased motion; (5) decreased joint swelling. It must be added that these patients probably could not get much worse, so we looked for positive findings. They were cases on whom many forms of therapy had been tried with no improvement.

In the tabulation of the results, we have five major headings (see chart 1). The end results are rated none, poor (1 to 25 per cent), fair (25 to 50 per cent), good (50 to 75 per cent) and excellent (75 to 100 per cent). In judging in which column a case should be placed in the tabulation of results, if there were negative findings to all the criteria as stated above, the case would be placed in the no improvement column. A poor result would be one in which perhaps two or three positive results appeared out of the five suggested ratings, such as feeling better and loss of pain. In the fair group, the result would be judged by the possibility of feeling better, increased weight and increased motion, with loss of pain. Of course this can only be relative, as motion may not have improved in all the joints, but there may have been more motion in the shoulders, fingers, neck or knees. In the group rating called good, 50 to 75 per cent, one would find positive improvement in all five criteria on evaluation, considering most important partial loss of joint swelling and increased range of motion. The gain of weight and subjective symptoms of pain and feeling better are all added. In the last group, we have the cases which are marked excellent, showing 75 to 100 per cent improvement and these patients have shown improvement in every respect. There are two cases which were completely relieved. However, they are left in the excellent group.

The conclusions drawn from these orthopedic examinations and evaluations of the patients treated by vitamin D show that the greatest improvement appeared in the patients with rheumatoid arthritis. One noteworthy finding was that there was considerable improvement in four cases of Marie-Strümpell arthritis. This improvement was in the muscles of the neck and shoulders. However, the changes in the spine were not improved because

ankylosis had taken place. It might be considered that the improvement in the osteoarthritic patients was of no particular note.

This report is upon 42 cases examined out of the possible 50 which are reported from the clinical angle in Dr. Snyder's section of this paper. The eight other cases to complete the series were not available and thus my statistics have to be based upon the cases examined.

CHART I

Classification Type of Arthritis	End Results				
	None	Poor 1–25%	Fair 25–50%	Good 50–75%	Excellent 75–100%
Osteoarthritis	3		2		
Rheumatoid arthritis	5	2	18	2	5
Marie-Strümpell arthritis			4		
Bursitis (chronic)	1				
Total	9	2	24	2	5
Per cent	21.42%	4.76%	57.12%	4.76%	11.90%

42 cases examined at one year intervals. Deductions from findings such as

(1) feels better
(2) increased weight
(3) loss of pain
(4) increased motion
(5) loss of joint swelling.

Discussion on paper of Dr. Snyder et al., "The Treatment of Arthritis with an Agent Containing Massive Doses of Vitamin D"

DR. CHARLES A. RAGAN, JR., New York City: At the Arthritis Clinic of the Presbyterian Hospital, New York, we had 31 cases. These patients were admittedly a difficult group of cases. Most of them had had gold and had developed some manifestations of intoxication, so we could not give them gold. One developed agranulocytosis. Four had the disease for less than two years. A woman of 27 had the disease for more than three years. None of them had it for less than a year. The treatment was not so prolonged as in Dr. Snyder's cases. We continued the drug only for four months in 11 patients, in eight patients for four to six months, and in 12 for more than six months. We did serum-calcium determinations on these patients and found no elevation after treatment. In nine there was an elevation above 11.9. Eighteen of the patients developed some toxic manifestations, usually nausea and vomiting, which promptly cleared after cessation of the treatment.

As far as improvement goes, we were struck by one feature of the drug, namely that seven of the patients felt very much better. In only one patient could we see any objective signs of improvement. Seven showed a significant drop in sedimentation rate; eight were promptly improved but the result was not very striking. Sixteen showed no improvement at all. One remained well after he stopped the drug. The remainder relapsed immediately after the drug was discontinued. In view of the

report from Hopkins regarding the use of irradiated ergosterol we are hesitant to continue the use of this medication.

DR. DARRELL C. CRAIN, JR., Washington, D. C.: I wonder if some one might have a little influence with the publicity departments of the manufacturers of the products that are used. Many of us have been getting advertising from the manufacturers of concentrated vitamin D which could be described as "enthusiastic," to put it mildly. Some well controlled experiments by other investigators would seem to indicate that concentrated vitamin D is not the super cure for rheumatoid arthritis that some are claiming. Certainly the general practitioner who gets some of the advertising put out by the Ertron Company might be led astray if he were to take it seriously. I think in all fairness to the medical men throughout the country Dr. Snyder might suggest to this company that it be a little more objective in its advertising.

DR. CLYDE HARTZELL KELCHNER, Allentown, Pennsylvania: Last April I enjoyed the privilege of seeing some of these patients whom Dr. Snyder was treating with Ertron. They were very much more enthusiastic about Ertron than were our patients at the Abington Memorial Hospital Arthritis Clinic. There was also some difference in the type of patient as well as in the type of treatment used in the two clinics. Dr. Snyder's patients were entirely pay patients, whereas ours were charity patients with a lower economic status. Ertron was the only treatment given his patients, but our group received rest, dietetic and physical therapy as well as all the usual, accepted forms of antiarthritic treatment, in addition to Ertron. Their focal infections were cleared up conservatively and we tried to correct their anemia as well as any other derangement of their physiological processes.

In our small group of 40 cases under Ertron therapy for 12 to 24 months, we had 22.5 per cent who said that they were better, although the sedimentation rate of these atrophic arthritics had not returned to normal levels. Another 22.5 per cent said that although their arthritis was no better, they felt much stronger while they were taking Ertron; 30 per cent were no better; 15 per cent refused to continue with the Ertron therapy (three said it made their arthritis worse; one refused it because of severe anorexia and marked weight loss; a fifth complained of severe headaches; and a sixth of sharp abdominal pain). There were four patients, or 10 per cent, in whom we stopped it because we were afraid to continue the Ertron. One patient, a man of 42, developed a coronary occlusion which may not have been influenced in any way by the Ertron. Two other patients developed a marked leukopenia during the course of Ertron therapy, one of whom developed a peculiar skin lesion which the dermatologists thought might be caused by an allergic reaction. Another patient showed a rise in blood phosphorus to 13 and phosphatase to 24 and we were afraid to give her any more. In all fairness to the drug, I must say that all of our 40 cases were severely involved atrophic arthritics.

DR. RICHARD H. FREYBERG, Ann Arbor, Michigan: I have been interested in hearing these reports. For the last three years we have been studying the effects of various preparations of vitamin D administered in large doses, including the preparation Dr. Snyder reported on. Our results were not so good as Dr. Snyder's. We followed 36 patients with rheumatoid arthritis, for at least two years and some as long as three years. Those 36 patients were given 45 different courses of treatment. Only 14 patients were considered to have had subjective improvement. Some of these reported considerable improvement but had only slight subjective improvement. There were only six instances of objective improvement among these patients. In only 16 per cent of cases was there a reduction in the erythrocyte sedimentation rate. We felt that only in the minority of patients was there any evidence of improvement in the course of the disease. There were a number of instances of gastrointestinal

irritation with anorexia and vomiting due to the medicine. In eight patients significant hypercalcemia developed and in many instances this was accompanied by quite severe symptoms. So we are not very greatly impressed by the evidences of improvement.

We wished to see whether or not some of the improvement might be on a psychogenic basis. Through the courtesy of the manufacturers of one of the preparations employed, capsules containing a placebo were made. These placebo capsules were given some patients for approximately two months before administration of vitamin D. Some patients who had subjective improvement with the vitamin D had no improvement when the placebo was given. We concluded that in the majority of cases the symptomatic improvement, where it occurred, was not on a psychogenic basis.

At this time we feel that evidence of improvement from large doses of vitamin D as we employed it is rather slight and occurred in only a minority of the patients. One mistake that many physicians are apt to make is to rely upon a single drug for the treatment of arthritis, so that little or nothing else will be done for these patients. We feel that this preparation certainly should not be relied upon as a remedy which will alter the course of the disease; less than half of our patients had symptomatic improvement, and considerably fewer had any objective evidence of improvement.

Dr. R. Garfield Snyder, New York City (closing): My purpose in presenting this paper on the treatment of arthritis with an agent containing massive doses of vitamin D was not to emphasize the value of any one type of vitamin D, but rather it was an attempt to arouse renewed interest in the use of massive doses of vitamin D in the treatment of arthritis.

Although our entire experience has been limited to the study of one particular type of vitamin D, it is obvious that the entire subject needs careful study, not only in one clinic but in many clinics, and that in the future comparative studies should be made of the various types of vitamin D to determine which one, if any, is the most efficacious and least toxic.

In this study we only used one therapeutic agent. Although it is necessary to do this from a scientific standpoint, it is hardly fair to any therapeutic agent to use it alone, for most agents should be used in combination with other well known therapeutic agents in order to get the maximum beneficial effect.

It has been brought out here this afternoon that at Presbyterian Clinic, Abington Memorial Clinic and the University of Michigan Clinic various degrees of improvement were obtained; most of the observers claim that they did not see as good improvement as we reported in our series. The fact that different clinics obtained various percentages of clinical improvement is not of great importance, because many uncontrollable factors enter into the question of relative degree of improvement obtained in any one clinic. For example, Dr. Kelchner visited our clinic recently and observed a very distinct difference in the class of patients we were treating and those treated in his clinic. Our clinic is a pay clinic; the patients are intelligent and very coöperative, whereas the patients in the Abington Clinic are charity patients. In the University of Michigan clinic the patients come from long distances throughout the state, so that they cannot return for frequent careful observation.

There is no reason why the clinical improvement should be absolutely uniform with this therapeutic agent, any more than they are uniform with gold.

In regard to the subject now under discussion, it is possible that they did not obtain a large percentage of good results at Presbyterian because of the fact that they only had a small series and did not keep up the treatment long enough. We have found from experience that many cases do not start to improve until the second or third month after treatment is instituted.

In regard to the toxic results reported from Johns Hopkins, it should be noted that they had only two cases. The vitamin D product used in these two cases was

only 50 per cent calciferol, and the remaining 50 per cent was made up of toxic side products. In addition, the dosage used in these cases was 700,000 units per day, which is almost three times what we found to be safe in our clinic with a much less toxic product. It seems strange to me that this report should even be published in the Journal of the American Medical Association. Certainly, a series of two cases is obviously too small a series on which to base any reliable conclusions, especially as all the toxic symptoms cleared up within two days.

The moving picture demonstration was presented as a new method of establishing objective improvement in a series of arthritis cases treated by a new therapeutic method. In view of the skepticism which always is associated with the introduction of a new form of treatment, we feel that this method of establishing unquestionable visible evidence of improvement should be used more frequently in the future.

In conclusion, we admit that we do not know how this form of vitamin D acts, and we do not know that massive doses of vitamin D are really necessary in order to cure arthritis. At the present time we have no known way of estimating the amount of vitamin D that is actually absorbed, as there is no chemical method to determine how much vitamin D is eliminated in the feces and the urine. It may be possible that most of it passes through the intestines unchanged. For that reason we have had this product prepared in such a manner that we can inject intramuscularly, so that we will actually know in the future how much vitamin D it is necessary to inject in order to obtain therapeutic results in arthritis.

We also admit that we do not know from previous experience that this particular product is better and less toxic than the vitamin D preparations made by the ultraviolet method. During the coming year we intend to carry out a very careful comparative study of another series, using vitamin D prepared by the ultraviolet irradiation method.

TREATMENT OF ARTHRITIC CONTRACTURES OF THE KNEE

(Abstract)

By JOHN G. KUHNS, M.D., *Boston, Massachusetts*

DEFORMITIES at the knee are among the most disabling of deformities in chronic arthritis. Five hundred and eighty-six contractures at the knee (313 patients) were found in 1453 patients suffering from chronic arthritis on the Wards of the Robert B. Brigham Hospital. A contracture is defined as a relatively fixed shortening of a group of muscles and their ligaments. After it has been present several years it often leads to irreversible changes in the muscles. Flexion contractures of less than 10° were not included in this study since, as far as could be observed, little disturbance in function resulted from so mild a deformity at the knee joints.

Extension contractures were recorded only if the knee could not be flexed more than 10° from the fully extended position. This type of contracture was observed only when the knee was kept in extension for long periods of time during the active stage of the disease, or when much force had been used in correcting a previous flexion deformity.

All of the contractures except 11 followed involvement of the knee by atrophic arthritis. Eleven flexion contractures occurred as the result of

hypertrophic arthritis. Usually both knees were similarly involved in the same patient, but there were 40 patients with flexion contracture in one knee and no deformity in the other knee. The case histories of these patients suggested that local trauma played the major part in this involvement of one knee only.

In attempts to prevent and to correct these contractures of the knee, a program of treatment was evolved which has been modified as more effective methods have been found. In patients seen during the first six months of their arthritis, contractures could usually be prevented.

The most effective method of preventing contractures at the knee when arthritis was present was rest in full extension until the muscular spasm and pain had subsided. Walking was permitted when motion and weight-bearing did not lead to pain. If the period of rest was prolonged beyond two weeks, exercises were often necessary to maintain strength and control of muscles about the knee. Splinting of the knee in extension was required if there was a persistent tendency to flexion. Fixation was not continued longer than one week without examining the knee and permitting a little motion temporarily. Long fixation of the knee without motion tended to produce extensive muscular atrophy and a contracture in extension.

When a flexion contracture could not be corrected passively, an attempt was made to correct it by a series of plaster casts. With the fixation of a plaster cast the muscular spasm usually subsided and the knee could then be brought into more extension. The plaster cast was cut into an anterior and posterior half in two days and was removed for short periods to permit the application of heat and for exercises when these could be performed without pain. When 10 degrees or more of correction in the contracture had been obtained a new cast was applied. Contractures were usually corrected by this method in from one to three months. For persisting weakness of the muscles of the thigh a caliper was then worn when walking to maintain correction until the muscles became stronger.

The results of treatment are listed as good with a final result of less than 5° of contracture; fair with from 5 to 15° of contracture remaining; and poor when there were more than 15° of persisting contracture. Many of the contractures of long duration and of severe degree required surgical correction. There is no satisfactory method of determining the resistance of contractures at the first examination. One can tell whether plaster casts will be effective usually only after several weeks of trial.

This study showed:

1. Arthritic contractures at the knee can be prevented: (1) by rest, if weight-bearing causes pain; (2) by splinting the knee in full extension, if there is muscular spasm; and (3) by exercise, if there is muscular weakness and atrophy.

2. When flexion contractures cannot be corrected passively the best early method of correction is a series of plaster casts, each cast securing as much

extension as possible. Calipers and exercises are usually required after full correction in order to maintain it until muscular strength is regained.

3. Flexion contractures too resistant for plaster casts are corrected most easily by a posterior capsuloplasty. It leads to painless weight bearing if the articular surfaces are not destroyed.

4. Manipulation, wedging casts and traction are relatively ineffective procedures. Skeletal traction is of value only after operations which free the contracture and permit extension gradually or the correction of a subluxation.

5. Arthroplasty is the procedure of choice in ankylosis if motion is desired. In chronic arthritis the end results to date have rarely been good. Osteotomy is employed when a better position for weight bearing alone is desired.

Discussion on paper of Dr. Kuhns, "The Treatment of Arthritic Contractures of the Knee"

DR. FRANK D. DICKSON, Kansas City, Missouri: Dr. Kuhns has not been guilty of over-statement when he says that contractures of the knee constitute one of the serious after results of arthritis. Such contractures do lead to very serious incapacitating disability.

In his discussion Dr. Kuhns has very wisely differentiated between contractures of limited duration and those that have existed over a long period of time. In the former we are dealing with tissues which are still plastic and more or less readily corrected. In the latter we have to do with ligaments which are fibrosed, thickened, and unextensible so that they not only resist efforts at correction, but tend very definitely to reproduce deformity even though this has been corrected by one of the methods which Dr. Kuhns has enumerated.

In cases of acute arthritis our experience parallels that of Dr. Kuhns in the desirability of maintaining the limb in extension in a plaster splint until the acute symptoms have subsided. This requires a number of weeks, as a rule. Then after the acute stage has subsided, it is desirable to remove the extremity from the splint and exercise the joints very gently, applying hot fomentations before such movements are carried out.

In older cases with fixed contractures, we are dealing with a different problem entirely. Deformities in these cases must first be corrected and such correction maintained or they will recur. Although I would admit that often and perhaps generally in these older cases, correction can be secured by a series of corrective plaster splints, our experience with this method has not been so happy as to cause us to use it extensively. Our failures have been due perhaps to lack of patience on our part. We prefer to do a capsuloplasty in these older, resistant cases rather than to attempt correction either by traction or casts.

In our experience forced manipulation has been of no value in resistant contractures. It can only add to joint damage and usually results in ankylosis in extension. There is one exception to this: in mild flexion contractures in which the joint is quiescent, I believe in such cases wedge casts properly handled are highly effective.

I cannot agree with Dr. Kuhns when he says that traction is not an effective method of correcting contractures. Compound traction or Russell's contraction acts very well, particularly in young individuals. I believe its value should not be overlooked.

Osteotomy, we feel, has an unimportant place in the treatment of arthritis and contractures of the knee.

Arthrodesis is a very useful procedure in badly damaged knee joints if the hip joint is not involved and the other knee is serviceable. So often both knees are involved that I must agree with Dr. Kuhns that arthrodesis has not a large field of application.

In the final analysis, prevention is always better than correction and usually easier of accomplishment. The best treatment for a fully contracted knee is to begin treatment early, prevent deformity from occurring and so avoid the necessity of reconstruction surgery.

I want to thank Dr. Kuhns for the thorough manner in which he handled this important subject.

DR. W. P. HOLBROOK, Tucson, Arizona: I could spend the entire time allotted for discussion of this paper in enumerating the points upon which I agree with Dr. Kuhns, so I shall limit my discussion to a few things upon which I do not agree.

First of all, let me raise the point with regard to selecting a suitable time for straightening, manipulation or doing capsuloplasties on flexion contractures of the knee.

I had always been told by my orthopedic colleagues that one should wait until the disease was inactive and until the joint was quiescent. This practice resulted in the accumulation of many stubborn flexion contractures which never became entirely inactive, even after waiting for months and sometimes years.

About 1935 my associate, Dr. Hill, and I decided to see how important this factor was and what would happen if correction of flexion contractures was carried out regardless of disease activity. We selected 19 patients with flexion contractures whose disease was obviously active, for trial. Under deep anesthesia, manipulation was carried out for the purpose of correcting the flexion deformity. These were patients who had failed to correct their deformity with the cast process which Dr. Kuhns described. Four patients required two manipulations to secure correction; four required capsuloplasties, the balance were straightened by simple manipulation on the first attempt. Fourteen of these 19 patients were rechecked a year later and found to be walking with straight legs. Since this time we have done many such manipulations with equally satisfying results.

I wish to emphasize the point that waiting too long for activity of the disease to subside will end in more stubborn contractures and that the sooner a flexed joint is straightened the more satisfactory is the ultimate result.

We fully approve of a period of relaxation in corrective casts, but if the leg does not straighten very promptly within a few weeks or months, more drastic procedure should be carried out without delay.

This brings me to the second point which concerns the value of manipulation in which I seem to be in disagreement. Soft, gentle manipulation will restore many of these flexion contractures to a perfectly straight leg without the necessity of dangerous manipulation or capsuloplasty.

Until manipulation has been attempted under deep anesthesia, it is impossible to tell whether the deformity will be corrected fairly easily or not. Our results with manipulation have been so satisfactory in general that we have done fewer and fewer capsuloplasties.

The third point upon which I wish to disagree is the question of the degree of correction necessary in a flexion contracture. I agree that if you have a 60 or 80 degree knee flexion contracture and will reduce it to 15 degrees, you have placed the leg in a position in which the patient may be able to walk, but if you allow walking on a 15 degree flexion contracture, very shortly that contracture will become 20 or 25 degrees. The flexion contracture will recur and the patient will again become bedridden.

We have felt that even a 5 degree flexion should be watched most carefully before allowing much walking. If possible, we carry our correction of the contracture to

where the leg comes back to complete extension and the entire group of hamstring muscles are relaxed and not taut.

The fourth point is that one must be very careful in allowing walking even with a very small degree of contraction until sufficient time has elapsed for healing and an adequate course of corrective muscle exercises completed. If weight bearing is allowed too soon, before muscle tone is sufficient to maintain weight in the erect position, flexion invariably recurs.

The last point concerns the occasional loss of flexion following a manipulation or operative procedure. Most of these occur because of failure to begin passive and assistive exercises early enough. We have had relatively few in this group and those were in joints so badly destroyed that the manipulative procedure was done without much hope of securing a moveable joint.

I wish to thank Dr. Kuhns for such a timely and scholarly paper.

Dr. Edward F. Hartung, New York City: I would like to ask Dr. Kuhns if one case he showed did not have a posterior dislocation of the tibia. This brings up a very important point. In our experience the main disadvantage of any form of correction except posterior capsulotomy is the great frequency of a sequential subluxation of the tibia. In our experience, unless the correction is attempted within the first year and unless the deformity is very slight, almost any form of correction except an open operation will result in a subluxation. In severe and long standing flexion deformities at the knee the only effective treatment is posterior capsulotomy. An additional observation we have made is the inability of the patient to extend the leg completely even after an open operation, owing to the lengthening of the quadriceps as a result of the prolonged flexion deformity. We commonly meet this situation by transplanting the tibial tuberosity distally.

Dr. Loring T. Swaim, Boston, Massachusetts: I personally feel that many of these corrective things should never have to be performed. Our real job is to get these cases early and treat them adequately by prevention so that we will not have to resort to operative or manipulative procedures to get them corrected. If we could get the cases early enough the possibility of flexure contraction would be taken into consideration in the very beginning and prevented at the start.

Dr. John G. Kuhns, Boston, Massachusetts: I am very grateful for the disagreement of opinion. I think you will see that as there was much disagreement among those who treat acute rheumatism, there is just as much disagreement among those who treat flexion contractures.

In regard to the manipulation, we begin just as with any correction and as we did with the changes of casts which I have described.

As to the question of arthrodesis being a useful procedure, in the past few months I have seen four patients who had arthrodeses performed by general surgeons who came into our clinic with arthritis in the other knee and in the back. What was I to do? There was nothing left to do.

I was enthusiastic about manipulation at first. When I first went to the Robert Breck Brigham, Dr. Swaim was very kind to me and permitted me to manipulate a number of flexed knees. Most of those knees are stiff in extension and I am not certain whether it would not have been better to leave them as they were with a little motion in flexion.

A mild flexion contracture is not always disabling. I have had several old ladies who would not submit to operative procedures in whom I have attempted corrections. I have been working on those knees for a matter of five years or more and there has been no appreciable change. Probably if I took roentgenograms I would notice some lipping. Probably there would be trouble in the back. That lantern slide to which Dr. Hartung referred did not show a subluxation of the tibia. If you have a flexion deformity of more than 30° it may look like a subluxation.

THE TOCOPHEROLS (VITAMIN E) IN THE TREATMENT OF PRIMARY FIBROSITIS

By CHARLES LEROY STEINBERG, M.D., *Rochester, New York*

THE therapy of primary fibrositis has been most unsatisfactory, and there is no unanimity of opinion regarding it. Previous communications have called attention to the similarity in the pathologic lesions between so-called nutritional muscular dystrophy and primary fibrositis. Mackenzie and McCollum have shown that the development of nutritional muscular dystrophy is accompanied by an increase in urinary creatine excretion, and improvement by decrease in urinary creatine.

Creatine excretion studies were done on 15 cases of primary fibrositis by the Folin microchemical method. After tocopherol therapy these studies were repeated on 13 cases. The creatine excretion was increased in all cases before therapy was started. The total amount of creatine varied from 264 to 918 mg. The creatine was increased above 300 mg. in 12 cases. Tocopherol therapy had a marked effect in reducing the urinary creatine excretion. In one instance the creatine dropped from 750 to 95 mg. after one week of therapy, in another from 495 to 110 mg., and in another instance the creatine excretion dropped from 706 to 196 mg. after seven weeks of tocopherol therapy. The daily urinary creatine excretion varied from 86.4 to 140 mg. daily in a control group of ten normal individuals. Two cases of progressive muscular dystrophy had urinary creatine excretions of 504 mg. and 329 mg. respectively.

One hundred forty-five cases of primary fibrositis have been treated successfully with the tocopherols (vitamin E). The preparations, dosage and method of administration were as follows: Sixty cases of primary fibrositis were given daily by mouth for the first week 200 mg. of natural mixed tocopherols in oil, which was equivalent to 180 mg. in vitamin E activity expressed as alpha tocopherol. Half of this dosage was given thereafter. Ten cases of primary fibrositis were given 200 mg. of alpha tocopherol intramuscularly at weekly intervals along with the oral treatment. Thirty cases of primary fibrositis were given 2 to 8 c.c. of wheat germ oil daily by mouth. Twenty-one cases of primary fibrositis were given 200 mg. of alpha tocopherol intramuscularly at weekly intervals. Nine cases of primary fibrositis were given 334 mg. of mixed natural tocopherols intramuscularly at weekly intervals. This preparation caused severe local reactions in all instances and systemic reactions in three instances. The local reaction consisted of localized pain, increase in local heat and swelling. The local lesion healed leaving a firm fibrotic area. No suppuration occurred. The systemic reaction consisted of increased generalized aches, soreness and slight increase of temperature. This reaction was later traced to the presence of about 18 per cent of vegetable sterols in the preparation. These sterols, of course, are entirely unobjectionable orally, but are not readily

assimilated by tissue. Nine cases of primary fibrositis were given 65 mg. of alpha tocopherol succinate, six cases the same amount of gamma tocopherol palmitate three times daily by mouth. One hundred forty-three out of the 145 cases treated in this manner were completely relieved of all symptoms in a period of from one to three weeks after starting therapy. Two cases that received wheat germ oil were only slightly improved. Four cases were treated by inunction with the natural mixed tocopherols without benefit.

A careful history and physical examination are carried out to establish or refute a diagnosis of primary fibrositis. A biopsy or urinary creatine determination or both are done on questionable cases. Three hundred mg. of the natural mixed tocopherols in oil are given daily by mouth during the first week. Half this dose is given for the next two to three weeks. Bile salts along with oral tocopherol therapy have been given to a recent group of cases studied. It is too early to evaluate results from this therapy. Sixty mg. of natural mixed tocopherols in oil are given daily by mouth for an indefinite period after complete recovery. This dose is maintained with the idea that the daily requirement of this vitamin is in the neighborhood of 1 mg. per kilo of body weight. Some of our patients have been observed for a period of 16 months under this management. No toxic effects have been noted.

Discussion on paper of Dr. Steinberg, "The Tocopherols (Vitamin E) in the Treatment of Primary Fibrositis"

K. HICKMAN, Ph.D., Rochester, N. Y.: I should warn you that I am not a medical doctor but a physical chemist who has become interested in vitamin technology. My firm prepares fat-soluble vitamins by high-vacuum distillation in the same town in which Dr. Steinberg lives. Our research laboratory has been experimenting on vitamin E for some years and we have had the privilege of sending various vitamin compounds to Dr. Steinberg who has applied them in his work.

Apparently primary fibrositis is the first human deficiency condition which has been found definitely to respond to vitamin E. This is in contrast with the doubtful response of human maternity cases to this vitamin.

I shall use the limited time at my disposal to describe certain aspects of the chemistry of vitamin E rather than to discuss Dr. Steinberg's paper directly. The vitamin was discovered 20 years ago by Evans and co-workers as a material which would cure an artificially induced sterility in rats. It was at once assumed that the vitamin should play a similar part in human medicine, curing *naturally-occurring* sterility conditions and particularly female abortion. Similar hopes were entertained for vitamin E in farm animal nutrition. These hopes have been partially realized in the latter case but have failed to materialize in human medicine.

In spite of these failures, it was evident that vitamin E, which occurs in nearly all foods and especially in fats and in tissues near the seed or reproductive organs, must have some important function. It was already known that vitamin E is the usual natural preservative of fats which quickly go rancid unless they contain 1–10 parts in 10,000 of the vitamin. It occurred to us that perhaps the vitamin preserves not only the fat but the body tissues in contact with fat and the oil-soluble vitamins contained in the fat and the tissue. This belief was strengthened by Moore's observation that the quantity of vitamin A found stored in the liver of the rat is proportional to the amount of vitamin E in the diet.

We have conducted experiments on the synergy of vitamin E with vitamin A and carotene. The method has been to test the increase of rate of growth induced by vitamin A or carotene when differing amounts of vitamin E are given simultaneously. The synergy turns out to be very pronounced, a quantity of carotene which is insufficient to support life in the absence of vitamin E becoming entirely adequate in the presence of the optimum quantity of E. On the other hand, in the complete absence of carotene the vitamin E is unable by itself to support life.

The synergy of these two oil-soluble vitamins is an important but isolated phenomenon. To make out a proper case for vitamin E, other related instances must be found. Dr. Steinberg has shown that vitamin E controls the quantity of creatine degraded from human muscle; experiments which we are sponsoring at the Strong Memorial Hospital in Rochester are showing that the vitamin E minimizes the destruction of vitamin A during juvenile fevers. If the present cures of fibrositis collected by Dr. Steinberg can be repeated with vitamin E elsewhere, it will be evident that the vitamin is playing as important a part in controlling the metabolism of muscle fiber as in controlling the survival of creatine and the fat-soluble vitamins. It suggests that vitamin E should be considered in other rheumatic and neural conditions in which other factors may be wasting in the absence of the vitamin. It is significant that the content of vitamin E in the modern diet is less than half that it is likely to have been in the diet of primitive man.

I have one minor criticism of Dr. Steinberg's paper which is that he has necessarily applied to human medicine a technic which would not be tolerated in the biological laboratory. He has striven for 100 per cent cures and since these have been obtained with doses of different magnitude, we can not tell from his present work what is the minimum curative dose of vitamin E. My belief is that this dose will prove to be smaller than that used by Dr. Steinberg, especially when the dosage is spread over every meal rather than given once daily. This smaller dosage, relatively unimportant clinically, may be significant where the vitamin has to be administered to those in straightened circumstances.

Dr. H. M. Margolis, Pittsburgh, Pennsylvania: Fibrositis, a condition met so frequently in practice, has received altogether too little study. Therefore, any additions to our understanding of this disease and especially any suggestions toward improving its treatment are indeed welcome. Dr. Steinberg's report raises several questions. In view of the biopsy findings and the creatine excretion changes, one gets the impression that the cases under consideration in this report are examples of true muscular fibrositis or muscular rheumatism. For it would be remarkable if vitamin E induced such an effect on the metabolism of tendinous structures, with alteration of the creatine excretion. One wonders, then, whether cases of so-called interstitial, capsular, or periarticular fibrosis have been included in this study.

In my own experience, true muscular fibrositis, with tender, palpable rheumatic nodules has been a rarity. By and large the cases of fibrositis we see are examples of capsular fibrositis, involving tendinous structures, in which we wish vitamin E were effective. It would, therefore, be helpful if Dr. Steinberg could tell us whether he makes such a diagnostic distinction between the various types of fibrositis and what his results have been in these different varieties of the disease.

Dr. M. H. Dawson, New York City: I should like to ask what are the clinical criteria on which a diagnosis of so-called "primary fibrositis" is made? The term is used so loosely that one cannot escape the conclusion that it is applied to a whole group of diseases including "psychosomatic rheumatism," bursitis, postural strain, occupational and traumatic conditions, etc. That such a variety of diseases should respond to one therapeutic agent seems fantastic.

DR. E. F. ROSENBERG, Chicago, Illinois: Dr. Steinberg has shown us photographs of severe Dupuytren's contracture, in illustration of a clinical form of fibrositis. Subsequently he has told us that he has been able to cure fibrositis in a large percentage of his cases with vitamin E. I would like to ask him whether he wishes to imply that severe Dupuytren's contracture can be cured by vitamin E.

DR. D. M. ANGEVINE, Wilmington, Delaware: I should like to ask three questions: (1) On how many patients were biopsies performed? (2) How many biopsies were done both before and after therapy? (3) Was the creatine tolerance determined on any of these patients?

DR. CHARLES LEROY STEINBERG, Rochester, N. Y. (closing): In reply to Dr. Hickman about scaling down the dose, there may be a revision of the dosage. The maintenance dose described by Mackenzie and his coworkers was 0.6 to 1.0 mg. per kilo of rabbit body weight.

Dr. Margolis brought up the question whether these cases were all muscular or periarticular fibrositis. It is difficult to be certain of the diagnosis of periarticular fibrositis in our experience. Later observation often proves these cases to be something other than primary fibrositis. All cases reported in this paper were fibrositis affecting muscle, tendon or aponeurosis.

Dr. Dawson asked by what criteria we make a diagnosis of primary fibrositis. The clinical history is most important. Given a healthy appearing individual whose muscles stiffen ("jell") on the least exposure to cold, who often must lose time from work because of generalized stiffness and soreness, whose blood picture is normal and who shows on careful examination of the skeletal structures, such tell tale evidences as fibrous nodules, thickenings in various planes of aponeuroses and tendon contractures without known cause a presumptive diagnosis of primary fibrositis should be made. If in addition, the urinary creatine excretion is increased and this creatinuria responds favorably to tocopherol therapy, then a positive diagnosis can be made. In other words, a diagnosis by exclusion is most important.

As to the question as to whether we have cured a case of Dupuytren's contracture, my experience is as follows: In no instance of marked contracture have we been able to improve the condition by medical methods. The skin of the palm of the hand is thick and leathery. Tocopherol therapy has returned this tissue to a more normal appearance. I have treated three early cases of Dupuytren's contracture involving one digit on each hand with tocopherol therapy and splinting the digit during the night. These three cases have markedly improved.

In reply to Dr. Angevine's question, 12 cases were biopsied. No follow-up biopsies on the treated cases were done.

CASE REPORTS

A CASE OF MULTIPLE MYELOMA WITH LIVER INFILTRATION AND A LOW PROTHROMBIN PURPURA *

By JOHN A. SCHINDLER, M.S., M.D., F.A.C.P., *Monroe, Wisconsin*

THIS case of multiple myeloma is being reported because of certain features that are rarely reported in the literature on multiple myeloma.[1] In half the cases of multiple myeloma the soft tissues, particularly the liver, spleen, and kidneys are invaded by the typical round cells closely resembling plasma cells and having little or no intercellular substance.[2] The case presented demonstrates such invasion and a resulting liver damage of such advanced degree as to give rise to most of the symptoms and signs the patient presented, most notably a purpura initiated by a low blood prothrombin.

CASE REPORT

W. K., aged 67, white, had always enjoyed extraordinarily good health, working daily as a carpenter. His family history was not revealing. His habits were good. He stated that he felt well until August 7, 1940, when he slipped and fell on his back while carrying a heavy piece of lumber. He felt an immediate pain in his back which, though not severe enough to disable him, continued as a constant soreness from that time on. It was not until three months later that he had any other soreness, and that began in his right anterior chest about December 1, 1940.

Within a week after his fall, he noticed weakness which began insidiously and gradually increased so that by mid-November, 1940, he had to stop work and by December 1, 1940, he was so weak as to be hardly able to walk.

Some time in August, too, a short time after his fall, he began to lose his zest for eating; he frequently felt nauseated, and he became more and more constipated. Even in October he noted an occasional black, sticky, foul stool. These symptoms increased in severity and by November 15, 1940, he could eat very little without feeling full; and vomiting, which consisted of recently eaten food, occurred almost daily. On November 16, 1940, he had a stool well mixed with bright red blood, and at frequent intervals more blood appeared, never in large amounts. His constipation by that time had become so severe that only large doses of castor oil produced a movement.

Never a heavy man, the loss of 20 pounds from August to December left him a very emaciated figure. He sought the aid of several physicians and clinics; his gastrointestinal tract was examined by roentgen-ray without finding any disease. He was placed by his last doctor on a high vitamin intake and iron for his anemia.

He entered St. Clare Hospital on December 12, 1940.

Physical Examination. The physical examination revealed a man well preserved for his years, quite emaciated, and able to a limited extent to walk around. His temperature was 98.8° F. orally, pulse 80, respiration 18, and blood pressure 130 mm. Hg systolic and 70 mm. diastolic. The positive physical findings were:

* Received for publication May 24, 1941.

(1) In both retinae were numerous scattered small recent hemorrhages. The blood vessels had a normal appearance. (2) There was a marked pallor to his skin and mucous membranes. (3) The gum margin showed oozing hemorrhages. There were petechiae scattered over the oral mucous membrane and over the skin on the thighs. (4) In the axillae and inguinal regions there were a few pea-sized elastic, movable lymph nodes. (5) The left eleventh and twelfth ribs were fairly tender to the touch as was one spot anteriorly on the right fourth rib. (6) There were fine râles scattered through the left posterolateral thorax. (7) The liver presented a smooth, rounded edge and extended three fingers' breadth below the right costal margin. The spleen was not palpable. (8) In the left costo-vertebral angle a hard smooth mass descended on inspiration. This could not be palpated laterally nor anteriorly. (9) Several enlarged, tortuous veins extended from the lower abdomen, over the costal margins and disappeared on the chest. The heart, prostate and neuromuscular systems presented no abnormalities.

The first diagnostic consideration was a differentiation between four widely varying conditions: (1) Hypernephroma with bone metastases, (2) cirrhosis of the liver, (3) carcinoma of the colon with metastases, and (4) leukemia or other blood dyscrasia.

The steps whereby the correct diagnosis was established will not be rehearsed. The first clue was found on the second day when a marked rouleaux formation of red blood cells was noted. With this guide post the establishment of the correct diagnosis was a simple affair.

Laboratory Data. The laboratory data gathered within a few days of his entrance to the hospital were: Red blood cells 1,480,000. Marked anisocytosis. Hemoglobin 3.8 gm. per cent. Hematocrit 12 per cent. White blood cells 5,000. Schilling differential count eosinophiles 1.0; basophiles 0; myelocytes 0; juveniles 0; stab. 13; segmented 33; small lymphocytes 51; large lymphocytes 2; monocytes 2. Bleeding time 14 minutes. Coagulation time 3 minutes. Prothrombin time (method of Quick) 56 seconds. Sedimentation rate 10 mm. per minute. Platelets 280,000. Fragility of red blood cells, beginning hemolysis 0.4 per cent, complete hemolysis 0.32 per cent. Takata-Ara test, positive. Hippuric acid synthesis 1.3 gm.; van den Bergh, slight direct reaction, 0.3 mg. per cent; non-protein nitrogen 44 mg. per cent. Urea 8 mg. per cent. Chlorides 490 mg. per cent. Total blood protein 6.83 gm. per cent. Calcium 6.04 mg. per cent (repeated). Phosphorus 5.0 mg. per cent (repeated). Gastric analysis fractional, free HCl of 49. Total acid of 86. Cevitamic acid 1.7 mg. per cent. Urine: specific gravity 1.012, albumin 3 plus, sugar 0; casts one plus, erythrocytes 3 to 4 plus, no Bence Jones protein. Bone marrow, sternal puncture, no marrow (repeated) but plasma-like cells in considerable number, having an abnormally large nucleus. So thin was the sternal plate that the hypodermic needle easily fell through it while infiltrating with novocaine.

Roentgenological. No defects of the skull were noted except a well circumscribed loss of density in the right mandible. The fourth anterior right rib, and the eleventh and twelfth left ribs showed punched out areas of rarefaction.

No defects of the spine and pelvis could be found.

The barium enema could not be introduced higher than the mid-sigmoid. At this point the barium column ended in a smooth constriction. The examiner classified the constriction as spastic rather than neoplastic.

Though the bones of the upper and lower arms were normal, all the long bones of the hands showed numerous punched out areas of decreased density.

Course. The patient was given 4 mg. daily of 1 methyl 1–4 naphthaquinone intravenously. In spite of this the prothrombin time did not deviate in the slightest. He was given B complex and cevitamic acid and a high carbohydrate intake by mouth. The rectal and urinary bleeding continued and six blood transfusions merely served to

raise his red blood count to 2,000,000. He appeared to be somewhat stronger and felt better, but on January 2, 1941 he suddenly became stuporous, his breathing stertorous, and examination revealed a complete paralysis of the entire right side. He died within a few hours.

Necropsy. The important features at the necropsy were a pathological fracture of the fourth right rib anteriorly. The liver was a pale granular grayish brown. In the colon were numerous hemorrhagic areas the largest of which were in the sigmoid, and here in two of the larger hemorrhages shallow ulcerations were present. Both kidneys were paler than normal with numerous small hemorrhagic areas scattered over the surface. The urinary bladder mucosa was highly hemorrhagic with old adherent blood clots in many places. In the brain were numerous small recent hemorrhages.

In the microscopic section of the liver, the sinusoids were dilated and literally packed with cells characteristic of the plasma cells of multiple myeloma. The liver cells themselves appeared fairly normal. In the kidney the venous capillaries were similarly filled with cells of the plasma type. In the marrow of the fourth rib the erythrogenic and leukogenic centers were entirely obliterated by an overgrowth of myeloid cells becoming plasma-like in numerous areas. In one of the inguinal nodes the sinusoids were filled with similar cells.

Comment

The rouleaux formation of the red blood cells which afforded the diagnostic sign post is thought always to occur with a hyperglobinemia. The total protein level here was 6.83 gm. per cent or normal. However, the albumin and globulin fractions were not separately done. In severe liver damage one may expect a marked inversion of the albumin-globulin ratio, not because globulin is increased, but because albumin is decreased. One can only conjecture whether a hyperglobinemia was present or not; certainly not one of very high grade.

The aggregation of red cells in rouleaux formation is doubtless in great part responsible for the extremely rapid sedimentation rate of 10 mm. per minute.

When an increased prothrombin time is not affected by intravenous injection of adequate amounts of synthetic vitamin K, critically severe damage of the liver has occurred. Severe liver damage in my experience is the only explanation of such a phenomenon. The clinical and laboratory evidences of liver damage in this case were enlargement of the liver, development of collateral circulation, a positive Takata-Ara test, a hippuric acid synthesis of 1.3 gm. and the prolonged prothrombin time not amenable to vitamin K therapy. That he died of the results of hemorrhage is definite. His course from the onset of his first symptoms to his death was a matter of only four months. The average duration of the disease was found by Geschickter [3] to be 24 months and by Batts [2] 24 months.

Though the blood calcium is by no means always increased in multiple myeloma, paralleling as it does the blood protein levels, it is distinctly unusual to have so low a figure as 6.04 mg. per cent. The patient had jerking and twitching, a positive Chvostek sign, but never went into tetany. I have seen similar low calcium figures in cirrhosis of the liver in which case it was usually accompanied by osteoporosis.

The high blood phosphorus is not unusual in multiple myeloma.

The question must necessarily arise whether such a case as this should be called a plasma-cell leukemia, the only criterion of which is the constant finding

of plasma cells in the blood,[4] or a diffuse plasma-cell myeloma. In this case no plasma cells were found in the circulating blood; it is possible the examination was insufficiently thorough. Until more is known of the origin of this type of cell, the classification is uncertain.

Clinically, this case is interesting since the patient showed four of the six cardinal symptoms and signs of multiple myeloma listed by Geschickter and Copeland[5]:

1. Multiple skeletal tumors in a person over the age of 35,
2. Spontaneous fractures, usually a rib,
3. Bence-Jones bodies in the urine,
4. Lumbar pain with early paraplegia,
5. Unexplained anemia.
6. Chronic nephritis with azotemia and low pressure, and yet these were overshadowed by the manifestations of purpura, the bleeding gums, hemorrhagic retinae, melena, hematuria, and skin and mucosal petechiae. Next to purpura in clinical importance was the apparent obstruction of the sigmoid, which was found to be due to spasm at the site of the ulcerations into the hemorrhagic necrosis, and finally there was the clinical appearance of hepatic cirrhosis.

In regard to the liver, the cells of which appeared fairly normal, but the sinusoids of which are so densely packed by myeloma cells, it is interesting to note what measurable functions were and were not impaired. The excretory function, as judged by the absence of jaundice and a van den Bergh of 0.3 mg. per cent was unimpaired. The most marked impairment was the inability to utilize vitamin K in the formation of prothrombin, etc. The formation of urea (8 mg. per cent) was likewise impaired.

Summary

1. A case of multiple myeloma is presented in which a striking invasion of the liver sinusoids by plasma-cells had occurred.

2. The most prominent clinical aspect of the patient was a marked purpura.

3. The purpura was due to a low blood prothrombin which was unaffected by large intravenous doses of 2 methyl 1–4 naphtholquinone.

4. Other clinical and laboratory evidences of severe liver damage were found.

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BALL THROMBUS IN THE HEART *

By David M. Spain, M.D., *New York, N. Y.*

Ball thrombus in the heart is a frequently mentioned complication in the course of mitral stenosis. However, reviews of the literature by Abramson (1914) [1] and Aronstein and Neuman (1939) [2] revealed reports of only 31 authentic cases. Recently, Garvin (1941) [3] reported three additional cases. Ball thrombus of the heart is rare, and in only a few cases has the correct antemortem diagnosis been made or even considered.

In the laboratories of pathology at Bellevue Hospital during the past year, I have encountered a ball thrombus in which the correct clinical diagnosis was made.

Case Report

The patient, (V. K.), a 33 year old white female housewife, was admitted on August 4, 1940 to the Fourth Medical Division of Bellevue Hospital (Dr. Charles Nammack, Director), following an episode of nocturnal dyspnea and cough with the production of pink frothy sputum. Ten days prior to admission the patient was hospitalized at another institution for cough and increased fatigability. After a few days of bed rest and sedation she was discharged as improved.

At the age of 15 she complained of "growing pains" but never had chorea or polyarthritis. Two years prior to admission she first noticed exertional dyspnea, orthopnea and cough. Since that time she had been on digitalis therapy.

Physical examination on admission revealed a thin, pale, young female with marked dyspnea and moderate cyanosis. Moderate dullness and fine to medium moist râles were present over the bases of both lungs, posteriorly. Examination of the heart showed a diffuse precordial heave, an apical systolic thrill and diastolic shock. The point of maximum impulse was in the sixth intercostal space, 3 cm. to the left of the midclavicular line. Regular sinus rhythm was observed and the sounds were of good quality. A localized harsh rumbling presystolic and a diffuse soft blowing systolic murmur were heard at the apex. The pulmonic second sound was louder than the aortic. The liver edge was felt 5 cm. below the costal margin.

While in the hospital the temperature varied between 99°–101° F. for the first three weeks and between 100°–103.5° F. during the last two weeks. Respirations averaged 26 per minute and pulse rate 95.

The sedimentation rate on August 21, 1940 was 41 mm. per hour and on September 4, 1940 was 48 mm. per hour. Several blood counts revealed an average result of white blood cells 13,000 with 78 per cent polymorphonuclear neutrophiles and 22 per cent lymphocytes, red blood cells 3.5 million with 68 per cent hemoglobin (Sahli). Urinalysis showed 1 plus albumin with occasional red blood cells and white blood cells. Five blood cultures were negative. Blood Wassermann reaction was negative and the blood chemistry showed nothing significant. Several electrocardiograms during the five weeks showed sinus rhythm, increased P-R interval, notched P-waves, inverted T_1 and diphasic P_1. Chest plate on August 20, 1940 showed marked interstitial fibrosis at the base of the right lung with thickening of the pleura in the costodiaphragmatic angle. The heart was enlarged in all diameters with fairly marked accentuation of the mitral curve. Chest plate on September 4, 1940 showed consolidation of the right middle and lower lobes.

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From the Laboratories of Pathology, Bellevue Hospital, New York City.

On August 7, 1940 there was a sudden onset of coldness and numbness of the right hand, the pulse was not palpable and deep cyanosis was present. Cardiac rhythm at this time was regular. Small petechiae were observed in the right conjunctiva. On August 8, 1940 no dorsalis pedis pulsation was evident and there was marked pallor over the dorsum of the right foot and left big toe. This episode was transient. On the evening of August 11, 1940 the patient suffered a coughing spell which was productive of a large quantity of bloody sputum. All the limbs at this time were warm and the pulses were felt except in the right foot where no dorsalis pedis pulsation was present.

On August 14, 1940 faint pulsation of the dorsalis pedis was noted. The chest showed diminished breath sounds at the right base. On August 18, 1940 all pulses were palpable. On several occasions there were transient episodes during which the patient

FIG. 1. Ball thrombus in left auricle.

complained of coldness of all four extremities and a slight faint feeling. No blood pressures were taken during these episodes because of their fleeting nature. On August 22, 1940 the patient suffered severe pain in the right flank and numerous red blood cells were detected for the first time in the urine. On August 30, 1940 the temperature rose to 103° F. the patient was coughing up bloody sputum and from this point on she became weaker and died on September 13, 1940.

The clinical diagnosis was rheumatic heart disease with mitral stenosis and insufficiency, pulmonary infarction, multiple embolic phenomena and ball thrombus of the left auricle.

Necropsy Findings. Necropsy was performed 15 hours after death. The peritoneal cavity contained a few hundred c.c. of clear straw-colored fluid. The liver extended 8 cm. below the costal margin. Seven hundred c.c. and 1,000 c.c. of clear straw-colored fluid were present in the right and left pleural cavities, respectively. Infarcts were present in the right lower lobe of the lung and both kidneys. The lungs showed congestion, edema and patchy bronchopneumonia.

The heart weighed 390 gm. The pericardial surfaces were smooth and glistening. On section the right auricle and ventricle were found to be considerably distended by postmortem clot. The right auricle was dilated and the right ventricle was both dilated and hypertrophied. The tricuspid valve appeared to be insufficient and was thickened and shortened. The pulmonary valve was normal. The left auricle was markedly dilated and its endocardium was thickened and roughened. Within this chamber was a roughly spherical, fairly smooth-surfaced, grayish-red mass, measuring 3 cm. in diameter. On section this thrombus consisted of partially organized, lamellated blood clot with a soft, red and necrotic center. It was attached to the posterior lateral surface of the auricle by a long, thin, friable pedicle. The thrombus lay loosely above the mitral orifice (figure 1). The mitral orifice was markedly stenosed as a result of thickening of the leaflets and shortening and fusion of the chordae tendineae. The orifice was likewise insufficient. The aortic valve appeared to be normal. The coronary ostia were widely patent and the vessels appeared to be normal throughout.

Comment and Summary

The left auricular endocarditis, in all probability, was the focus of origin for the thrombus, while the tight mitral stenosis was an important factor in its enlargement into a ball thrombus. The transient episodes of interference with the peripheral circulation were probably caused by intermittent partial obstruction of the mitral orifice by the ball thrombus. These episodes led to the consideration of ball thrombus as the causative factor.

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ENDOCARDITIS DUE TO *PSEUDOMONAS AERUGINOSA* *

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Pseudomonas aeruginosa (*B. pyocyaneus*) is a common saprophyte of the skin and gastrointestinal tract.[1] That it may also inhabit the urinary tract is suggested by its occasional isolation from the blood stream following urological operations.[2, 3] Being potentially pathogenic, it may invade from any of its usual locations, and cause serious localized or widespread infection. In rare instances localization on a heart valve has resulted in rapidly fatal acute endocarditis. Review of the literature shows only two such cases reported in this country [4, 5] and four in German medical literature.[6, 7, 8, 9]

Case Report

D. K., a diabetic white man, aged 66 years, entered the hospital because of general malaise, dyspnea, chills, and burning on urination. For three months he had noticed

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From the Department of Pathology, Saint Louis University School of Medicine.

progression in the severity of his nocturia, with burning and dribbling at the time of urination. Dyspnea had been present for two weeks. For four days the dyspnea had been severe, and accompanied by high fever, chills, headache and diarrhea.

He was a well developed man, without emaciation, and was rational and cooperative in spite of considerable dyspnea. The respiratory rate was 54 per minute, temperature 106° F., and pulse rate 104 per minute. His systolic blood pressure was 170 mm. of mercury, and diastolic 72 mm. The heart appeared slightly enlarged, though without thrills or murmurs. The rhythm was undisturbed except for occasional extrasystoles. Numerous râles were heard over both lungs posteriorly, and were coarser over the right base where the breath sounds were diminished and vocal fremitus increased. Some dullness on percussion was present posteriorly over the lower lobes.

By catheterization, 1,500 c.c. of urine were withdrawn from a distended and painful bladder, and a retention catheter left in place.

The laboratory findings at this time were as follows: *Urine:* acid; specific gravity 1.023; albumin 2+; sugar 2+; red blood count 3,810,000 per cu. mm.; hemoglobin 12 g.; white blood count 16,200 per cu. mm.; segmented forms 80 per cent; stabs 12 per cent; and lymphocytes 8 per cent; Kahn test negative; non-protein nitrogen 46 mg. per 100 c.c.; blood sugar, 238 mg. per 100 c.c.

FIG. 1. The heart, showing large vegetations on the mitral valve and some thickening of the chordae tendineae.

On the third day the patient was markedly dyspneic and delirious. The pulse was irregular and rapid. Bronchial breathing could be heard on both sides of the chest. Blood culture on the fourth and sixth days showed *P. aeruginosa*. On the seventh day the chest signs and general condition appeared improved.

The temperature rose again abruptly on the ninth day. The patient became dull and uncoöperative, and had involuntary bowel movements. Neck rigidity was noted, and the Kernig, Brudzinski, and Babinski tests were positive. Spinal fluid pressure was 45 mm. and on jugular pressure rose to 140 mm. The fluid was opalescent and had a cell count of 567 per cu. mm. Tests for globulin were negative, and no growth was obtained on culture.

The patient's condition steadily deteriorated. Blood culture taken on the fourteenth day again showed *P. aeruginosa*. Death occurred on the fifteenth day in hospital.

Autopsy Examination. The main findings at autopsy involved heart, lungs, meninges, and prostate. The heart weighed 300 grams. The mitral valve was thickened and retracted, with some areas of calcification and, apparently, a moderate degree of stenosis. The chordae tendineae were shortened, thickened, and firm. On the auricular surface of the valve were large, extremely friable, grayish vegetations (figure 1). There were areas of ulceration, but no actual perforation of the valve. Some of the vegetations extended onto the endocardium of the left auricle. The left auricle was considerably dilated. The cardiac valves, other than the mitral, were uninvolved.

Smears and sections from the mitral vegetations showed abundant, small, rod-shaped bacteria (figures 2 and 3), identified culturally as *P. aeruginosa*. Sections of the vegetations also showed large masses of necrotic debris and abundant fibrin. The myocardium was edematous and congested. In focal areas there were a few polymorphonuclear leukocytes between muscle fibers. In some areas coronary vessels were involved by inflammatory changes. The intima showed proliferative thickening, with some chronic inflammatory cells scattered through this portion of the arterial wall.

The lungs showed surprisingly little gross change. A hemorrhagic, infarct-like area about 1 cm. in diameter involved the lower part of the right upper lobe. The only other gross changes were subpleural, calcified, primary tuberculous lesions, and moderate anthracosis and emphysema. In sections, thrombi were evident in small arteries, and about the periphery of the area of necrosis there was fibrinous material and organization. Some alveoli about this region contained polymorphonuclear leukocytes.

Cerebrospinal fluid in the subarachnoid space appeared slightly increased in amount and cloudy. Between some of the convolutions in the region of the vertex it seemed almost purulent. Smears from this region showed many inflammatory cells, and a few small rod-like organisms similar to those from the cardiac vegetations. Cultures from the meninges showed *P. aeruginosa*. Microscopically, the cells in the meningeal exudate were predominantly polymorphonuclear leukocytes. The meningeal blood vessels were prominently involved, both veins and arteries being infiltrated by acute inflammatory cells (figure 4).

The urinary bladder had a thick edematous mucosa with some areas of hemorrhage. The prostate was considerably enlarged by adenomatous hyperplasia with areas of necrosis and abscess formation in which polymorphonuclear leukocytes were numerous and bacteria could be demonstrated (figure 5). Thrombi involved some of the periprostatic veins.

Small areas of focal necrosis were also present in the spleen. Areas of infarction and acute focal glomerular nephritis were evident in the kidneys. The gall-bladder wall was thickened, with chronic inflammatory cells in submucosa and muscularis.

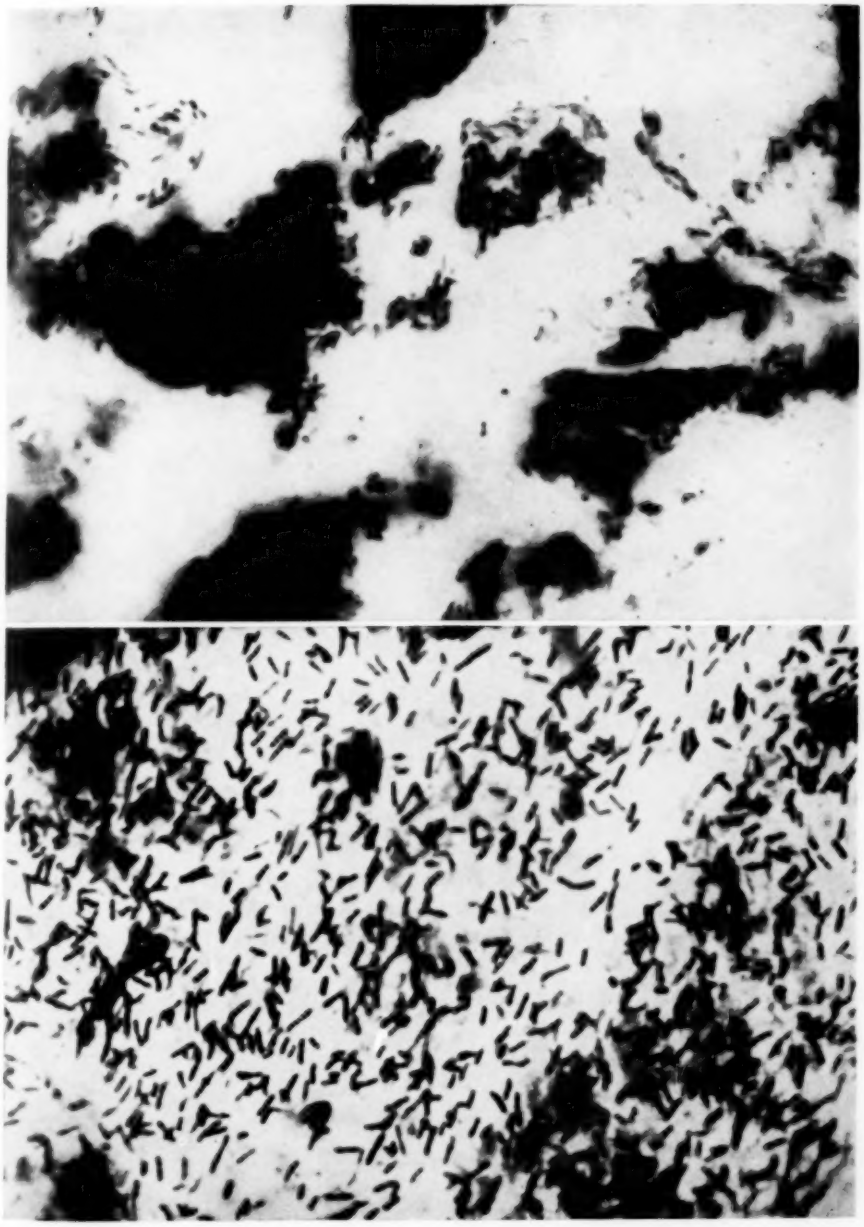

FIG. 2 (above). Microscopic appearance of the vegetations showing many large rods (Giemsa stain).

FIG. 3 (below). Smear from the vegetations showing the same large rods (Giemsa stain).

FIG. 4. Meningeal artery, showing infiltration of the walls with acute inflammatory cells (hematoxylin and eosin).

FIG. 5. Prostate, showing an area of suppuration forming an abscess (hematoxylin and eosin).

The final anatomical diagnoses were: acute bacterial mitral endocarditis due to *Pseudomonas aeruginosa;* old mitral endocarditis with calcification and stenosis; acute myocarditis; acute purulent meningitis; acute meningeal arteritis; infarcts of spleen, kidneys and lungs; acute focal glomerulonephritis; adenomatous hyperplasia of prostate; abscesses of prostate; thrombosis of periprostatic veins; chronic cystitis; acute splenitis; parenchymatous degeneration of liver and kidneys; chronic cholecystitis; hemangioma of liver; obsolete tuberculosis of lungs; mild generalized arteriosclerosis; fatty infiltration of pancreas (diabetes mellitus clinically); pyorrhea and dental caries.

Review of Previously Reported Cases: The six cases of endocarditis due to *P. aeruginosa* which have been previously reported are briefly noted here for the purpose of comparison. Details of these and the present case are given in the accompanying table. The literature was reviewed by Fish, Hand and Keim [5] in 1937. We have been unable to find any case reported since that time.

TABLE I

Tabulation of Cases of *P. aeruginosa* Endocarditis

Author	Blum[6]	De la Camp[7]	Rolly[8]	Thayer[4]	Bungeler[9]	Fish, Hand and Keim[5]	Moragues and Anderson
Age	2½ months	51	28	42	65	71	66
Sex	M	F	F	F	M	M	M
Valve involved	mitral	mitral	mitral	mitral	mitral	aortic	mitral
Previous damage to valve	?	?	yes	?	yes	?	yes
Probable portal of entry	?	skin?	gastro-intestinal tract	gastro-intestinal tract	contaminated intravenous injection	genito-urinary tract	genito-urinary tract
Other tissues involved	?	skin intestines spleen	meninges spleen kidneys arteries	peritoneum; intestines; ovaries	spleen	aorta kidneys	meninges, arteries, spleen, lungs, kidneys, prostate

Blum [6] in 1899 reported the case of a baby boy, two and a half months of age, with typical signs of congenital syphilis. At necropsy, a mitral endocarditis was found, with large numbers of Gram negative bacilli in the vegetations. These organisms were proved to be *P. aeruginosa.*

In 1903, a case of chronic pyocyaneus septicemia with polyarthritis and a hemorrhagic diathesis was recorded by De la Camp [7] in a woman, 51 years of age, who had also blisters, pustules and abscesses on the skin. The autopsy demonstrated bacterial endocarditis of the mitral valve. *P. aeruginosa* were isolated in pure culture from the vegetations.

In 1906, Rolly [8] published the case of a woman, 28 years of age, who had a typhoid-like septicemia two months before admission, during a small epidemic

in the house where she lived. She also had some meningeal symptoms. Cultures from blood and spinal fluid showed pure *P. aeruginosa.* At autopsy there was a bacterial endocarditis implanted on an old rheumatic mitral valve, meningitis and metastatic abscesses of spleen and kidneys. *P. aeruginosa* was demonstrated in sections of the valve and in the walls of the arteries.

Thayer,[4] in 1926, analyzed the case of a female, 42 years of age, admitted to the hospital with the complaints of diarrhea, vomiting, anorexia, and progressive asthenia, of about three to four weeks' duration. The temperature was subnormal, the pulse 100 per minute. The right leg was swollen and edematous, the superficial veins prominent, and palpable thrombi were evident in the saphenous vein. The diarrhea continued and the patient died seven days after admission. The autopsy revealed chronic pelvic cellulitis and peritonitis, an ovarian abscess and a recto-vaginal fistula. There were many ulcerations in small and large intestine with perforation and acute peritonitis; and in addition there was a gastric carcinoma. The heart showed bacterial endocarditis of the mitral valve. Cultures from the mitral vegetations, peritoneum, intestinal ulcers and ovarian abscess yielded pure growth of *P. aeruginosa.* This case occurred in the midst of a rather remarkable epidemic of Pyocyaneus disease with intestinal manifestations.

Bungeler,[9] in 1927, reported the case of a man, 65 years of age, who seven years before death had developed cardiac disease following erysipelas, and who showed physical signs of mitral insufficiency. Because of a "nervous disease" he was given repeated intravenous injections of a preparation of saprophytic bacteria called "saprovitan." This preparation was later proved to contain *P. aeruginosa.* He developed a septicemia and died after 16 days. The autopsy revealed bacterial endocarditis of the mitral valve with a perforation 1 cm. in diameter in one of the cusps. No histological or bacteriological study was made of the vegetations. Cultures from spleen yielded *B. proteus, P. aeruginosa* and Gram positive cocci in chains.

The case reported by Fish, Hand and Keim,[5] in 1937, was that of a male, aged 71, who entered the hospital because of inability to void for three days. He had been catheterized three times during the three days prior to admission. His urinary symptoms started 18 months previously when he developed acute retention. This recurred about every six months necessitating catheterization each time. Other symptoms were nocturia, slow stream and occasional dysuria. Examination disclosed a symmetrically enlarged prostate. There was trabeculation of the bladder with several diverticula. Fourteen days after admission a suprapubic prostatectomy was performed. On the seventh postoperative day his temperature suddenly rose to 103.4° F. Six blood cultures before death were all positive for *P. aeruginosa.* The patient died on the twenty-seventh postoperative day.

Bacterial endocarditis of the aortic valve with large numbers of Gram negative bacilli in the vegetations was found at autopsy. In the wall of the aorta there were inflammatory cells and Gram negative bacilli. The kidneys presented several infarcts and the prostate showed hyperplasia and several areas of acute inflammatory reaction though no bacteria should be demonstrated.

Comment

Consideration of the case reported here and of those already in medical literature discloses several points of interest. The portal of entry in the present case, as in that of Fish, Hand and Keim,[5] appears to have been the genitourinary tract, probably from a focus in the prostate. Hyman and Edelman [2] and Scott [3] have shown that *P. aeruginosa* may be isolated occasionally from the blood following urological operations. As in other types of bacterial endocarditis, there is a predilection for localization on a valve which is already damaged. Except in one case,[5] the mitral valve was the one involved. From the infected valve, spread may occur to spleen, kidneys, and meninges. Meningitis was a prominent manifestation in the present case as well as in that of Rolly.[8]

An interesting feature of infection with *P. aeruginosa* is involvement of blood vessels, particularly arteries. This vascular inflammation is well demonstrated in the case reported here (figure 4), and was observed also in the cases of Rolly [8] and of Fish, Hand and Keim.[5] This tendency of *P. aeruginosa* to cause vascular inflammation has been studied by Fraenkel.[1] The development of acute focal glomerular nephritis in association with this type of bacterial endocarditis does not appear to have been noted previously.

Summary

1. A case of bacterial endocarditis due to *Pseudomonas aeruginosa*, with meningitis, widespread infection of other organs and focal glomerular nephritis is presented.

2. The six other cases which have been reported are briefly summarized.

3. The importance of the genitourinary and gastrointestinal tracts as a portal of entry for *Pseudomonas aeruginosa* is pointed out. The tendency of this organism to cause acute vascular inflammation is noted.

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GONOCOCCAL MYCOTIC ANEURYSM OF THE AORTA: REPORT OF A CASE SUPERIMPOSED UPON A SYPHILITIC AORTA *

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MYCOTIC aneurysms involving the aorta and smaller arteries have been reported not infrequently in the literature. Various organisms have been isolated from the site of the aneurysm including the hemolytic and non-hemolytic streptococcus, staphylococcus, pneumococcus, *H. influenzae* and gonococcus. As a rule there is an associated endocarditis of the aortic or, less commonly, of the mitral valve, and it is supposed that the intima of the aorta becomes infected by secondary implantation from the valvular vegetations. A survey of the literature reveals nine cases of mycotic aneurysms resulting from gonococcal infection, which are summarized in table 1. We are reporting this case as the tenth such case. It is apparently unique, however, in that it is the only report known to us of a gonococcal mycotic aneurysm superimposed upon syphilitic aortitis.

CASE REPORT

T. F., a 41 year old Irish-American painter, entered the second medical service on January 27, 1939, complaining of joint and muscle pains of four weeks' duration. Twenty-five years previously he had been infected with syphilis and gonorrhea and over a period of several years had undergone irregular antisyphilitic treatment but received no specific treatment for gonorrhea. Seven years before, in 1932, he had been treated at the Boston City Hospital following a "shock" associated with unconsciousness for several hours and left hemiparesis. At that time he had no cardiac symptoms but there were well marked systolic and diastolic murmurs in the aortic area. The heart and great vessels were not enlarged by roentgenogram. The Kahn test for syphilis was positive in the blood and spinal fluid. Diagnoses of tertiary syphilis, syphilitic aortic regurgitation, and cerebral thrombosis were made. He was treated with intramuscular bismuth for about eight months until he stopped attending the clinic. At that time the Kahn test in the blood was still positive but the paralysis had entirely cleared.

Three years later he spent two days in the hospital following a prolonged alcoholic bout. At that time there was no change in the cardiac murmurs. There was no cardiac enlargement by roentgenogram, and the Kahn test for syphilis was negative in the blood and spinal fluid. An electrocardiogram was likewise normal.

During the succeeding four years he was free of symptoms and remained fairly steadily employed as a painter in spite of continued heavy drinking and an inadequate diet. In December, 1938, he began to have nocturnal attacks of suffocation and substernal pain associated with dyspnea and sweating. The pain often radiated down the inside of the right arm to the finger tips. After about a month of almost nightly attacks they began to diminish in frequency and severity but at the same time he began to have pain, redness, heat and swelling in the right foot and ankle associated with chills and sweats. Later the painful swelling extended to the muscles of the right hand. There had been no previous history of rheumatic fever or chorea.

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

On admission to the hospital the oral temperature was 104° F., pulse 120 and respirations 26 per minute. He was fairly well developed and nourished and in no acute distress. Dental caries was marked. The heart was not enlarged to percussion and the systolic and early diastolic murmurs previously noted were present in undiminished intensity. The radial pulses were equal. The blood pressure was 150 mm. Hg systolic, 70 mm. diastolic. A smooth tender liver edge was felt three fingers' breadth below the costal margin. The spleen was not felt. There were redness and swelling about the metacarpo-phalangeal joints of the right hand. There were also tenderness and pain on motion of the right shoulder joint. The prostate was enlarged, boggy and tender. There were venereal warts on the glans penis. The deep tendon reflexes

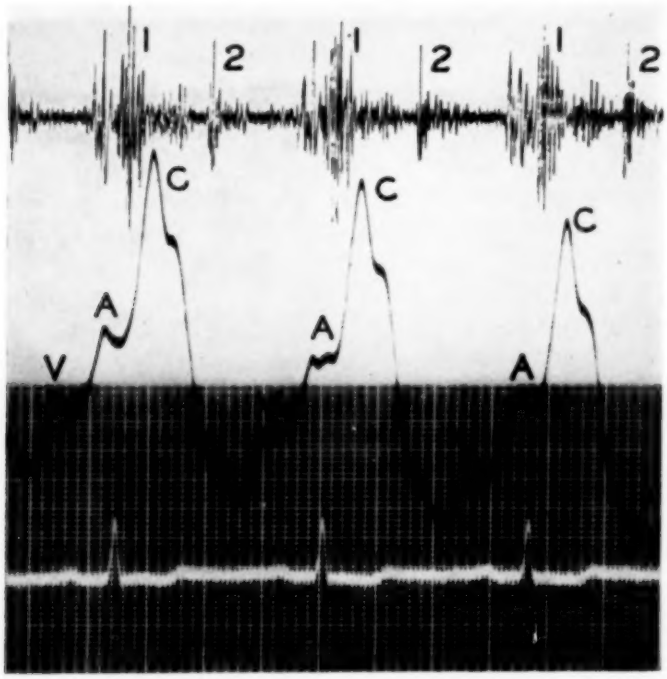

FIG. 1. Phono-electrocardiographic tracing taken just medial to the apex three weeks before death. The murmur preceding the first heart sound is the presystolic murmur and begins just prior to the peak of the A-wave. (We are indebted to Dr. E. A. Stead and Dr. Paul Kunkel for the use of this tracing.)

were hyperactive on the left. Laboratory findings were as follows: Blood hemoglobin 11.7 gm.; erythrocyte count 4,600,000: leukocyte count 19,000; with a differential of 72 per cent polymorphonuclear leukocytes, 7 per cent band forms, 15 per cent lymphocytes, 2 per cent monocytes, 3 per cent eosinophiles, and 1 per cent basophiles. Red blood cells and platelets were normal. Examination of the urine was negative except for 3–5 leukocytes, 2–3 epithelial cells, and an occasional red blood cell per high power field. There were no casts. Stool examination was negative for occult blood. The Hinton test for syphilis was positive in the blood as was a gonococcus complement fixation test. The non-protein nitrogen in the blood was 30 mg. per 100 c.c. and the total protein 6.5 grams. Agglutination tests for the enteric group of organisms and a prostatic smear and culture were negative. A roentgenogram of the chest and a retrograde pyelogram were likewise negative. An electrocardiogram was normal.

Course. During a period of 18 weeks in the hospital the patient had an irregular fever of 100° to 102° F. Because of a strong but unconfirmed suspicion that the infection was gonococcal in origin he was given three courses of sulfanilamide (6 grams per day). In each instance there was a temporary decline in fever with improvement which was not maintained in spite of continued treatment. Because of progressive secondary anemia, aggravated by the sulfanilamide, he was given three transfusions of 500 c.c. of whole blood. Eighteen blood cultures planted both aerobically and anaerobically were negative. The nineteenth and twentieth cultures, both taken five days before death, were reported positive for gonococcus after the patient had died.

The patient continued fairly comfortable, ambulatory, part time, for four months when he suddenly developed an attack of acute pulmonary edema apparently precipitated by a vomiting attack. This was the first sign of cardiac failure. At this time a distinct mitral diastolic crescendo murmur became audible at the apex (figure 1). Paroxysmal dyspnea and orthopnea became increasingly severe; edema of the extremities appeared, and there were severe nose bleeds and bloody stools. There were no petechiae. Three days before death the spleen became palpable. After 24 hours of progressive pulmonary edema, the patient died.

Necropsy Findings

Anatomical Diagnosis. Syphilitic aortitis with superimposed mycotic aneurysm (gonococcal). Lobar pneumonia, left lower lobe, type 17, with pleuritis. Syphilitic aortic valvulitis with aortic insufficiency. Septic infarcts of the spleen. Acute focal embolic glomerulo-nephritis.

The heart weighed 450 grams with enlargement primarily of the left ventricle. The tricuspid, pulmonary and mitral valves were normal. The commissure between the anterior and left posterior cusps of the aortic valves was widened so that there was a groove between the two cusps measuring about 0.6 cm. in width. The cusps were partly calcified in the region of this lesion so that it formed a rigid aperture which prevented the valve from closing completely. The leaflets and other commissures were normal. The endocardium of the left ventricle showed several fibrous plaques in the region of the aortic valve, these plaques being distributed in an oblique line across the endocardium beginning at the separation of the commissures mentioned above and ending at the lateral border of the left ventricle, seemingly marking the direction of the regurgitation of blood which probably occurred during life. The endocardium was otherwise normal. The aortic intima was covered with scattered lesions of two varieties, one consisting of irregular, raised, yellow plaques averaging 5 mm. in diameter and the other characterized by oval to round lesions cream-colored to white. For a distance of 9 cm. above the aortic valve the aorta was dilated having a circumference of 7.5 cm. while the more distal aorta, in which the raised plaques already described were more prominent, measured 5.0 cm. in circumference. Five centimeters above the aortic valve in the dilated portion of the aorta a spherical mass of grayish-red friable tissue was attached to the intima. When the mass was removed, a saccular aneurysm was revealed, the opening of which measured 1.5 cm. in diameter (figures 2 and 3). Friable grayish-yellow material was attached firmly to its margins and the sac measured 4 by 2 cm. It was filled with an old blood clot and impinged upon the left auricle. The left lung weighed 1340 gm. and the left lower lobe was consolidated and bluish-gray on cut surface.

The spleen weighed 380 gm. and was dark reddish-purple in color with an infarct measuring 5 cm. by 3 cm. extending to the surface and exuding yellow purulent material on cut surface.

The liver weighed 2,060 gm. The slightly enlarged kidneys had a combined weight of 380 gm. The capsular surface was smooth with a moderate number of

petechial hemorrhages over the surfaces of both kidneys and several dull red raised areas, the largest measuring 2½ by 2 cm. The prostate was of usual size and consistency without abscess or evidence of infection. The seminal vesicles and testes were negative.

Microscopic Examination. The heart muscle was normal. The alveoli of the left lower lobe of the lung were filled with polymorphonuclear leukocytes and fibrin.

FIG. 2. Photograph of the heart and aorta. A. Mycotic aneurysm. B. Deformed aortic valve with separation of the commissure. C. Roughened fibrous plaque.

There were multiple areas of focal necrosis with polymorphonuclear leukocytes throughout the spleen. The epithelium of the rectum was absent over a wide area. The glomeruli of the kidneys showed focal necrosis, infiltration with polymorphonuclear leukocytes and a marked proliferative capsular reaction in many instances with a few epithelial crescents. Many glomeruli showed almost complete hyalinization. The lymph nodes showed marked phagocytic activity in the germinal centers. In

sections of the aortic arch away from the mycotic aneurysm, there was marked fibrous intimal thickening of the aorta with interruption of the elastic tissue of the media and slight perivascular infiltration with lymphocytes in the media and adventitia. A

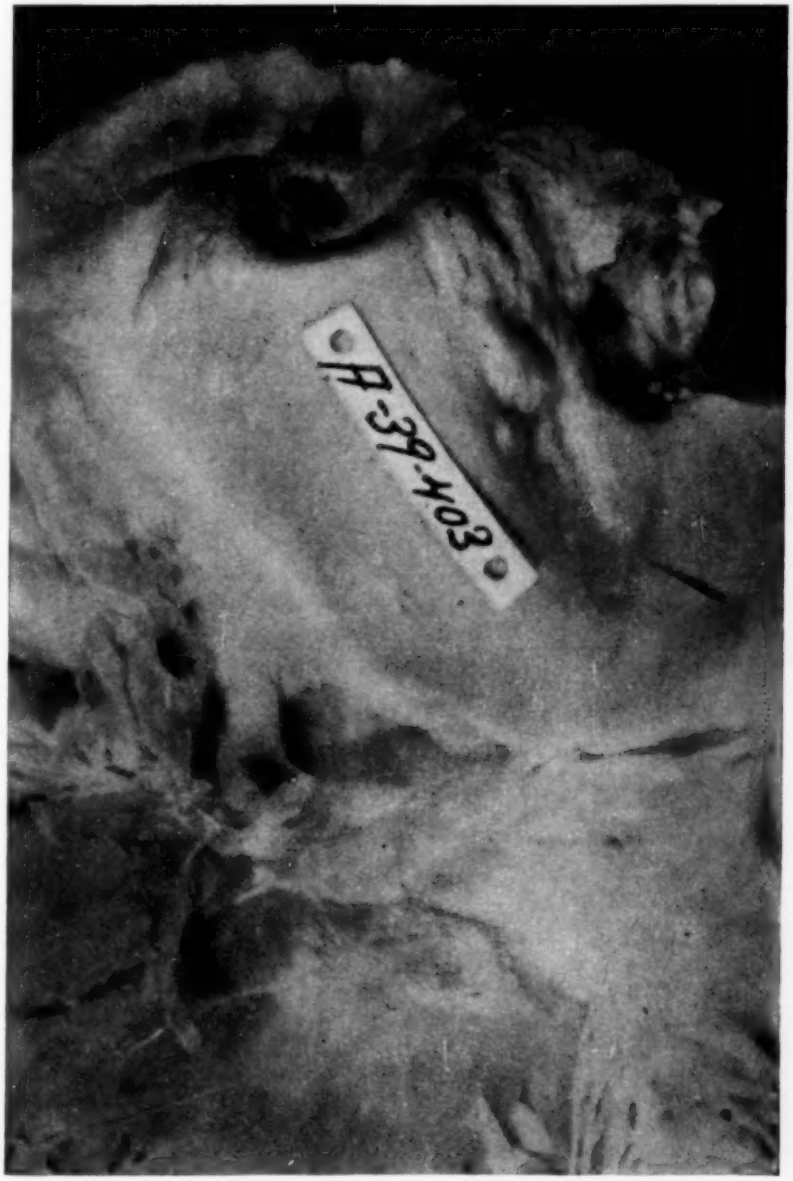

FIG. 3. Photograph of the aortic valve and aorta including the mycotic aneurysm.

section from the edge of the aneurysmal sac showed acute inflammatory infiltration consisting of polymorphonuclear leukocytes and fibrin in the intima and muscularis. There was acute necrosis involving both these areas. Rare diplococci could be seen

among the infiltrated cells. A section through the aneurysmal sac revealed complete absence of the intima and muscularis. The wall consisted of dense fibrous tissue, the surface of which was covered with young granulation tissue infiltrated by polymorphonuclear leukocytes and covered by fibrin. No elastic tissue was seen with elastic tissue stains in the aneurysmal sac. The vegetations consisted of a mass of fibrin, polymorphonuclear leukocytes and partly hyalinized material.

Bacteriology. Pneumococcus type 17 was obtained from the heart's blood. The spleen yielded gonococcus in pure culture. Vegetations from the mycotic aneurysm grew out both gonococcus and pneumococcus type 17. Cultures from the lung showed pneumococcus type 17 and *Staphylococcus aureus.*

Discussion

This case is of interest from three points of view: first, as a problem in clinical diagnosis; second, as throwing some light on the problem of the causation of the Austin-Flint murmur; and, third, as an example of a rare condition, mycotic aneurysm of gonococcal origin involving a syphilitic aorta.

Table I

Reported Cases of Gonococcus Mycotic Aneurysm of Aorta

Author	Date	Sex	Age	Endocarditis			Pericarditis	Positive Blood Culture During Life	Gonococcus Complement Fixation Test
				Chronic Valvular Disease		Bacterial Endocarditis			
				Location	Type	Acute			
Holst	1901	M	24	Mitral	Rheumatic	0	0	not taken	not done
Koster	1910	M	17	0	0	0	+	not taken	not done
Thayer	1922	M	28	Aortic and mitral	Rheumatic	0	0	negative	not done
Lindau	1924	F	38	Aortic and mitral	Rheumatic	0	+	negative	not done
Riefenstein	1924	F	29	0	0	+ (aortic)	+	negative	+
Riecker	1925	M	22	+	"Mild thickening"	+ (aortic)*	0	+	not done
Thibau	1929	M	18	+	"Mild thickening"	+ (aortic)	+	+	not done
Aschner	1932	F	23	Aortic and mitral	Rheumatic	0	+	+	+
Hoyt and Warren	1938	F	28	0	0	+ (aortic)	+	negative	negative
Authors	1941	M	41	Aortic and aortitis	Syphilitic	0	0	+	+

* A single small friable vegetation on the aortic valve, which yielded a *Streptococcus hemolyticus* on culture, perhaps only a terminal lesion.

From the diagnostic angle it was considered probable that the patient was suffering from a gonococcus arthritis and the therapeutic response to sulfanilamide was thought to be to a certain extent corroborative. Gonococcus endocarditis was suspected and would have been considered as confirmed if the blood cultures had been positive during life. The etiology of the underlying heart

condition was a puzzle. A well-marked aortic diastolic murmur had been observed over a period of seven years without demonstrable cardiac enlargement. Although it did not seem probable that syphilitic aortic regurgitation could pursue such a completely benign course, this seems actually to have been the case. Whether as a result of treatment or not, the progress of the syphilitic lesion in the aorta appears to have been arrested for this prolonged period.

In this case a well-marked mitral diastolic crescendo (Austin-Flint murmur) developed under observation. It is noteworthy that this murmur developed in the absence of an increase in the transverse diameter of the heart and without recent structural change in the aortic valve. The roentgen-ray measurements of the heart shadow on January 1, 1935, showed a cardiothoracic ratio of 14.5/29.8, whereas on May 15, 1939, after the development of the murmur, it was 14.4/29.1. It is difficult therefore to explain the development of the Austin-Flint murmur on the theory of a dilated left ventricle leading to relative mitral stenosis. On the other hand, the absence of postmortem evidence of recent structural alteration in the aortic valve might seem to militate against the theory that this murmur of recent origin could be entirely ascribed to the effect of a regurgitant stream from the aorta impinging upon a mitral leaflet thus causing, in effect, a stenosis. The development of the murmur coincident with the onset of failure suggests that the altered circulatory dynamics associated with failure were responsible. Chief among these factors were an increased venous pressure and a shortened diastolic filling time (electrical systole was prolonged by 0.06 sec.).

Mycotic aneurysm is an occasional complication of bacterial invasion of the blood stream. The aorta is the artery most frequently involved but the abdominal vessels, the cerebral arteries and the arteries of the extremities are also attacked in the order named. Formation of a mycotic aneurysm is the result of lodgement of bacteria in the arterial wall with destruction of elastic fibers producing a local weakness. Aschner lists five routes by which organisms may reach the arterial wall, namely:

"(1) By direct extension from suppuration in adjoining structures, aneurysm par arrosion.

(2) By extension to or implantation upon the intima from endocarditis of the aortic cusps; endocarditis verrucosa, or ulcerosa. This may occur in a previously normal or atherosclerotic aorta.

(3) Metastatic aortitis, verrucous and ulcerous; infection by way of the blood stream implanted upon the intima from a distant focus. Here also the aorta may have been previously normal or atherosclerotic.

(4) Embolo-mycotic aortitis; embolic infection through the vasa-vasorum of the aorta by way of the coronary arteries. As bacteria may also reach the aortic wall by this route we may speak of metastatic mycotic aortitis. The source may be the heart valves or some distant focus.

(5) Lymphogenous aortitis as in cases secondary to purulent pericarditis or lymphadenitis."

It is evident that in this case the mode of development must have been as suggested under number three or metastatic ulcerative aortitis. The primary focus was not found at autopsy but it seems likely from a review of the course of the patient that the distant focus probably was the arthritis which had been present a few months before death.

SUMMARY

The reported cases of gonococcal mycotic aneurysms of the aorta are reviewed and an unusual case of a gonococcal mycotic aneurysm involving a syphilitic aorta is presented. The diagnostic difficulties encountered and certain unusual auscultatory findings are discussed.

We are indebted to Dr. Kenneth Mallory for valuable assistance in preparing this report. We are also indebted to Miss Marion Lamb and to Dr. Ashbel Williams of the Mallory Institute of Pathology for the bacteriological and anatomical findings, respectively.

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EDITORIAL

IMMUNITY FROM INFLUENZA AND POSSIBLE METHODS FOR ITS PRODUCTION

The term influenza has been used customarily to indicate a clinical syndrome rather than a clear cut etiological entity. The usual clinical manifestations of "influenza" are familiar to all our readers: the abrupt onset with fever, malaise, prostration, generalized aches and pains, signs of irritation of the respiratory mucous membranes which are often slight in comparison with the systemic symptoms, a leukopenia and usually a high degree of contagiousness. Illness of this type may occur in great pandemics, as localized epidemics which may have a high morbidity within the area involved, and as sporadic interepidemic cases, commonly called "endemic influenza."

Definite evidence as to the etiology of influenza has been obtained only regarding a portion of the epidemic cases. Smith, Andrewes and Laidlaw [1] in 1933 first succeeded in isolating a filtrable virus by intranasal inoculation of ferrets with nasal secretion of human cases. These findings have been confirmed in many parts of the world, and there is no doubt that this virus, now designated influenza A, has been the cause of a large proportion of the cases in most of the recent epidemics which have been carefully studied. In 1940 Magill and Francis independently isolated another virus, influenza B, which serologically is entirely different from A, although the diseases they incite are otherwise indistinguishable. Finally there is a third group amounting on the average to about one-third of the epidemic cases, "influenza Y," which are not caused by either virus A or B. Nothing positive is known as to the cause of these cases, and they are best regarded as a miscellaneous aggregation which may or may not be due to one or more different viruses.

The relative frequency of these types has varied greatly in different epidemics, and all three have been found in a single epidemic. Virus A has been reported more frequently than B, but the latter was the principal cause of the epidemic in 1940, and it appears also to be widespread. It has been reported in England and in Australia.

Nothing positive is yet known as to the cause of pandemic influenza. There are many reasons for suspecting that it is caused by a virus, but this is still only an inference and it must remain so until another pandemic appears. The status of the sporadic cases is still more questionable. No virus has yet been obtained from them.

Recovery from an attack of epidemic influenza is followed by an immunity, but this is less effective and less enduring than that observed after many other virus diseases. This lack of immunity is at times more apparent

[1] SMITH, W., ANDREWES, C. H., and LAIDLAW, P. P.: A virus obtained from influenza patients, Lancet, 1933, ii, 66.

than real. In some individuals successive attacks have been due to antigenically different types of virus, and no one type affords any protection from infection with any other type. Several instances have been reported, however, in which virus A was isolated in two and even three successive attacks in the same individual at about two year intervals. Minor antigenic differences between various strains of A virus have been described, but the significance of these differences is still uncertain.

Studies on experimental animals (ferrets, mice) and man have furnished much information regarding the infection, although a great deal remains obscure. The present status of the problem has been well summarized by Horsfall [2] and by Francis.[3] Two discoveries of fundamental technical importance have greatly facilitated these studies. The first was the demonstration that chick embryos are highly susceptible to infection, and to a considerable extent can replace ferrets and mice for the demonstration of the virus, and even for its original isolation from patients. They also afford a convenient means of furnishing virus in large amounts and in relatively pure form.

The second was the observation of Hirst [4] that active virus causes agglutination of chicken red blood cells and that this agglutination is specifically inhibited by immune serum from man or animals. The procedure can be used for titrating the potency (antibody content) of such sera. The results are sufficiently close to those obtained by testing the protective power of the serum in mice to warrant its use in extensive epidemiological studies.

In both man and animals the portal of entry of infection is the respiratory tract. The tissue primarily attacked is the superficial ciliated epithelium, and infection is largely limited to this and to its supporting tissues. Virulent strains cause pulmonary consolidations in animals, but this is not an essential part of the disease and appears to occur rarely if at all in uncomplicated infections in man. The virus has never been found in the blood in man, and generalized systemic infection does not occur. Parenteral injections of virus do not reproduce the disease, either in man or animals. They do stimulate the development of immunity in animals, associated with the appearance of virus-neutralizing antibodies in the blood. The immunity seems to be somewhat less effective and less permanent, however, than that following recovery from infection caused by intranasal inoculation.

In man, also, recovery is accompanied by the appearance of circulating antibodies. In general the degree of protection afforded varies directly with the antibody content of the serum. In man the incidence of infection during an epidemic is greater in those with an initially low antibody titer. The

[2] Horsfall, F. L., Jr.: The present status of the influenza problem, Jr. Am. Med. Assoc., 1942, cxx, 284–287.

[3] Francis, T., Jr.: A rationale for studies in the control of epidemic influenza, Science, 1943, xcvii, 229–235.

[4] Hirst, G. K.: The agglutination of red cells by allantoic fluid of chick embryo infected with influenza virus, Science, 1941, xciv, 22–23.

relationship is not precise, however, and no quantity has been found which is certain to prevent infection in all individuals.

Since there is at least an approximate relationship between the virus-neutralizing power of the serum and resistance to infection, it was obviously desirable to determine whether injections of virus in man would increase the activity of the serum sufficiently to afford protection. Several extensive experiments of this type have been reported [2, 5] in which virus was administered, usually subcutaneously, a few weeks before the outbreak of an epidemic. In general there was a fairly satisfactory increase in titer of antibodies in the serum of those individuals who had had but little initially. On the other hand, if the titer was originally high, it was but little affected by the vaccination.

The results were less satisfactory, however, as far as actual protection from infection is concerned. In some series no definite reduction in the incidence of infection in the vaccinated group could be demonstrated. In others the incidence of infection was significantly reduced from the statistical standpoint, but on the average by only one-third to one-half as compared with the control groups. From the practical standpoint, this is not satisfactory.

Stokes and Henle,[5] however, reported more successful results in a group of 100 boys, of whom 72 had been vaccinated with a chick embryo virus inactivated by formaldehyde, and 28 were untreated controls. All were allowed to inhale an atomized virus suspension of considerable virulence. Ten of the controls developed clinical influenza, whereas only one case appeared in the vaccinated group. A considerable number in both groups, however, showed a slight elevation of temperature and presumably had subclinical infections.

Two factors may in part explain these relatively unsatisfactory results. The virus given may have been excessively attenuated, and the parenteral route of administration may be an unfavorable one.

The virus, in penetrating and attacking the superficial epithelium, is not directly exposed to the antibodies in the circulating blood. Antibodies presumably could protect from infection only if they were within or on the surface of the cells. Burnet studied human nasal secretion from this standpoint, and found that it had definite virus-neutralizing power, although quantitatively this was much less than that of the blood serum. Furthermore there was a direct relationship between the activity of the blood serum and that of the nasal secretion, and the latter was likewise increased by immunization. It is also reasonable to suppose that the resistance of the cells might be more effectively increased if they participated directly in the process of immunization, that is, if the virus, suitably attenuated, were administered intranasally in the hope of causing a subclinical infection. Burnet showed that this is the case in animals.

[5] Stokes, J. Jr., and Henle, W.: Studies on methods of prevention of influenza, Jr. Am. Med. Assoc., 1942, cxx, 16–20.

Burnet[6] in 1940 reported an experiment with 17 human volunteers. An attenuated vaccine was sprayed into the nose on two occasions at one week intervals, and then an active virus was instilled into the nose and throat. Three subjects developed clinical influenza, and one other had a mild attack. Four others showed a rise in antibody titer which indicated a subclinical infection. All those who became ill had had low initial antibody titers in their serum. The attenuated virus, however, was virtually inert as it caused no rise in antibody titer except in one case.

Burnet[7] subsequently tried the effect of one nasal application of attenuated B virus in 22 volunteers. In nine cases with low initial antibody content in the serum the titer was substantially increased without any manifestation of clinical illness. He regarded this as evidence of increased resistance, but he did not report testing these cases with active virus.

Smorodintseff et al.[8] in 1937 reported the intranasal application of virus "attenuated" by passages through ferrets and mice in 72 volunteers. Of these, 14 subjects developed clinical influenza, one third had general symptoms and 40 per cent showed some nasal hyperemia and discharge. Those who developed infection all had had low initial antibody titers which rose markedly after recovery. Those with higher initial titers showed no signs of illness but may have had a subclinical infection as there was a "distinct and consistent" rise in titer, although this was less marked than in the other group.

Francis[3] has also reported applying an attenuated virus by intranasal sprays or packs without causing clinical disease but without obtaining a regular increase in circulating antibody. He did not mention direct tests for immunity in this group.

Manifestly no practicable procedure for immunization on a large scale can be mapped out on the basis of the experiments so far reported. They do suggest lines along which future experiments may be profitably conducted. If immunization is to be attempted, both A and B virus should be employed, and they should probably be administered by the intranasal route. The virus must be sufficiently attenuated so as not to cause severe infection in any appreciable number of the subjects, but it must retain sufficient activity to incite a subclinical infection in susceptible individuals. This obviously will require precise manipulation but the difficulties need not be insuperable. There appears, however, to be definite limitation to the usefulness of any immunization procedure. As already pointed out, the protection afforded by recovery from natural infection is often relatively transient, and it is not likely that better results can be obtained from any practicable method of artificial immunization. It would therefore seem to be useful

[6] BURNET, F. M., and FOLEY, M.: The result of intranasal inoculation of modified and unmodified influenza virus strains in human volunteers, Med. Jr. Australia, 1940, ii, 655–659.

[7] BURNET, F. M.: Influenza B virus. II. Immunization of human volunteers with living attenuated virus, Med. Jr. Australia, 1942, i, 673–674.

[8] SMORODINTSEFF, A. A., et al.: Investigation of volunteers infected with the influenza virus, Am. Jr. Med. Sci., 1937, cxciv, 159.

only in the face of an impending epidemic or in special situations in which even temporary protection would be important.

It is possible to secure immediate substantial although brief protection by passive immunization. Stokes and his associates have shown in animal experiments that protection can be afforded for about a ten day period by intranasal instillations of immune serum. By this route only from one-tenth to one one-hundredth as much serum is required as by parenteral injection. Smorodintseff et al.[9] have reported successful immunization by this method in man. During an extensive epidemic in Leningrad they treated 501 volunteers by intranasal administration of serum of highly immunized horses. Two doses were given at 15 day intervals. The incidence of infection was reduced from 8.2 per cent among 1825 controls to 0.4 per cent.

Such a procedure is no substitute for an effective method of active immunization. Until the latter has been perfected, however, passive immunization might be of real value, particularly in the presence of a rapidly spreading epidemic.

[9] SMORODINTSEFF, A. A. et al.: Über die spezifische Prophylaxie der epidemischen Grippe durch Inhalation antigrippösen Serums, Ztschr. f. klin. Med., 1940, cxxxviii, 756–765.

REVIEWS

Essentials of Pathology. By LAWRENCE W. SMITH, M.D., and EDWIN S. GAULT, M.D. Second Edition. 960 pages; 22.5 × 29 cm. D. Appleton-Century Co., Inc., New York. Price, $10.00.

This book on pathology as its name indicates is primarily designed to meet the needs of medical students and practitioners. It is not recommended for workers in the specialized field of pathology, since there are many volumes written on subjects which can only briefly be discussed in this text. Nevertheless it contains an excellent bibliography.

In general the orthodox and familiar arrangement of discussion is followed: (1) general pathology, (2) tumors, and (3) systemic pathology. This is in reality a handbook of pathology plus an atlas, and contains many excellent photographs and plates. In this second edition the first thirteen chapters which deal with fundamental pathological changes has been given more elaboration and space.

There are 295 complete case histories presented. The case history method of presentation and correlation of clinical and pathological changes is especially useful for the student. The microscopic descriptions are of great value in laboratory work. This method is not entirely new in textbooks on pathology since it was used by W. T. Councilman in 1912.

The book is larger than average and not of convenient size. Many blank pages are inserted for additional notes. Value of these pages is questionable as many book lovers are hesitant to mark up their valuable books. Also the margins are rather wide and add to the size of the volume.

The subject material on the whole is very well presented. The parasitic infestations are given adequate space. This is of especial importance now, and will be for some time to come because of the war and greater development in rapid transportation.

B. S.

BOOKS RECEIVED

Books received during May are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Aviation Medicine. By LOUIS HOPEWELL BAUER, M.D. Edited by HENRY A. CHRISTIAN, A.M., M.D., LL.D., Sc.D. (Hon.), F.A.C.P., Hon. F.R.C.P. (Can.). 50 pages; 24 × 16 cm. 1943. Oxford University Press, New York City. Price, $1.50.

Gout. By JOHN H. TALBOTT, M.D. Edited by HENRY A. CHRISTIAN, A.M., M.D., LL.D., Sc.D. (Hon.), F.A.C.P., Hon. F.R.C.P. (Can.). 55 pages; 24 × 16 cm. 1943. Oxford University Press, New York City. Price, $2.50.

Medico-Legal Blood Group Determination. Theory, Technique, and Practice. By DAVID HARLEY, M.D., B.Sc., F.I.C. 119 pages; 22.5 × 15 cm. 1943. Grune & Stratton, Inc., New York City. Price, 12 s. 6 d. net.

Clinical Roentgenology of the Cardiovascular System. Second Edition. By HUGO ROESLER, M.D., F.A.C.P. 480 pages; 26 × 17 cm. 1943. Charles C. Thomas, Springfield, Illinois. Price, $7.50.

Allergy, Anaphylaxis and Immunotherapy. By BRET RATNER, M.D. 834 pages; 23.5 × 16 cm. 1943. Williams and Wilkins Co., Baltimore. Price, $8.50.

The Physiological Basis of Medical Practice. Third Edition. By CHARLES HERBERT BEST, M.A., M.D., D.Sc. (Lond.), F. R. S., F.R.C.P. (Canada), and NORMAN BURKE TAYLOR, M.D., F.R.S. (Canada), F.R.C.S. (Edin.), F.R.C.P. (Canada), M.R.C.S. (Eng.), L.R.C.P. (Lond.). 1942 pages; 23.5 × 16 cm. 1943. Williams and Wilkins Co., Baltimore. Price, $10.00.

Your Arthritis. What You Can Do About it. By ALFRED E. PHELPS, M.D. With an Introduction by R. GARFIELD SNYDER, M.D. 192 pages; 19.5 × 13 cm. 1943. William Morrow & Co., Inc., New York City. Price, $2.00.

Essentials of Syphilology. By RUDOLPH H. KAMPMEIER, A.B., M.D. 518 pages; 20 × 13.5 cm. 1943. J. B. Lippincott Co., Philadelphia. Price, $5.00.

Skin Grafting of Burns. By JAMES BARRETT BROWN, M.D., and FRANK MCDOWELL, M.D. (Lt. Col., Med. Corps, A.U.S.). 204 pages; 26.5 × 18.5 cm. 1943. J. B. Lippincott Co., Philadelphia. Price, $5.00.

Vitamins and Hormones. Vol. I. (*Advances in Research and Applications.*) Edited by ROBERT S. HARRIS and KENNETH V. THIMANN. With a foreword by E. V. MCCOLLUM. 452 pages; 23.5 × 15.5 cm. 1943. Academic Press, Inc., New York City. Price, $6.50.

A Guide to Practical Nutrition. A series of articles on nutrition, sponsored by the Committee on Nutrition and Deficiency Diseases of the Philadelphia County Medical Society. Reprinted from Philadelphia Medicine, 1941–1942. Edited for the Committee by MICHAEL G. WOHL, M.D., and JOHN H. WILLARD, M.D. Introduction by MORRIS FISHBEIN, M.D. 98 pages; 24.5 × 17 cm. 1943. Philadelphia County Medical Society, Philadelphia.

COLLEGE NEWS NOTES

Additional A. C. P. Members in the Armed Forces

Already published in preceding issues of this journal were the names of 1,430 Fellows and Associates of the College on active military duty. Herewith are reported the names of 10 additional members, bringing the grand total to 1,440.

Marvin B. Corlette
Dolph L. Curb
Thomas H. DeLaureal
Harold Fink
Marshall W. Graham
Saul Jarcho
Robert M. Lintz
E. David Sherman
Brandt F. Steele
William D. Stubenbord

Tentative Program of Postgraduate Courses of the American College of Physicians, Autumn, 1943

In accordance with the policy of the College in furnishing to its members and medical officers in the armed forces opportunities for graduate instruction, the Advisory Committee on Postgraduate Courses has announced the following program for the autumn of 1943:

Course No. 1. Endocrinology (October 11–16) at Chicago under the directorship of Dr. Willard O. Thompson, F.A.C.P.; Fee, $20.00.

Course No. 2. Allergy (October 25–30) at Roosevelt Hospital, New York City, under the directorship of Dr. Robert A. Cooke, F.A.C.P.; Fee, $20.00.

Course No. 3. Special Medicine (November 8–19) at various Philadelphia institutions under the directorship of Dr. Charles L. Brown, F.A.C.P.; Fee, $40.00.

Course No. 3, Special Medicine, will be an unusual course in that it will be given, not at a single institution, but at most of the leading medical institutions in Philadelphia, including special days and special subjects at Temple University School of Medicine, University of Pennsylvania School of Medicine and Graduate School of Medicine, the Pennsylvania Hospital, Jefferson Medical College of Philadelphia, the Phipps Institute, the Philadelphia General Hospital, the Institute of the Pennsylvania Hospital, the Lankenau Hospital, the Hospital of the University of Pennsylvania, and the Philadelphia City Morgue. Subjects covered will include psychosomatic medicine, allergy, arthritis and related conditions, blood diseases, cardiovascular diseases, peripheral diseases, syphilis, gonorrhea, respiratory diseases, tuberculosis, gastrointestinal diseases, chemotherapy, diagnostic roentgenography, psychiatry, metabolic problems, tropical medicine, tumors, and legal medicine.

The course will conclude on Friday, November 19, which will be devoted to a Regional Meeting of the College for Pennsylvania, New Jersey, Delaware, and adjacent territories. Members of the College committees and the Board of Regents will be present to take part in the Regional Meeting, which will include, in the morning, medical clinics at the Hospital of the University of Pennsylvania under Dr. O. H. Perry Pepper, F.A.C.P.; at noon, a buffet luncheon at the College Headquarters; in the afternoon, a general session with papers by eminent authorities; and, in the evening, a social hour and dinner meeting at one of Philadelphia's leading hotels.

Gifts to the College Library

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members:

Reprints

Dr. Lyman B. Carruthers, F.A.C.P., Miraj, S.M.C., India—3 reprints;
Dr. Harold R. Carter (Associate), Denver, Colo.—1 reprint;
Dr. Herbert R. Edwards, F.A.C.P., New York, N. Y.—13 reprints;
Jack D. Kirshbaum (Associate), Major, (MRC), U. S. Army—19 reprints;
Dr. Vincent W. Koch, F.A.C.P., Janesville, Wis.—1 reprint;
Aleksei A. Leonidoff, F.A.C.P., Lieutenant Colonel, (MRC), U. S. Army—1 reprint;
Benjamin H. Neiman (Associate), Major, (MRC), U. S. Army—1 reprint;
Frank B. Queen, F.A.C.P., Lieutenant Colonel, (MRC), U. S. Army—1 reprint;
Dr. David Salkin, F.A.C.P., Hopemont, W. Va.—1 reprint;
Dr. Leon Schiff, F.A.C.P., Cincinnati, Ohio—1 reprint;
Dr. Leon Schwartz, F.A.C.P., Medical Officer of the Bureau of Census—"The Health Program of the United States Bureau of the Census";
Dr. R. S. Anderson, F.A.C.P., Erie, Pa.—"Annual Report for 1942 of the Erie County Tuberculosis Hospital."

Southeastern States Regional Meeting

The American College of Physicians held a Regional Meeting at Jacksonville, Fla., May 26, 1943, for the States of Florida, Georgia, Alabama and South Carolina. The program has been published in a previous issue of this journal. An analysis of the attendance showed a total of 146, of whom 84 were Service physicians and 62 were civilian physicians. Of this number, however, 72 were members of the College, and 74 were guests, chiefly from the Medical Corps of the Army and Navy in the district. The member attendance was 23.9 per cent for the territory, which, though considerably lower than the average for Regional Meetings which heretofore has been about 40 per cent, was nevertheless a good showing, due to the acute war conditions in that part of the country.

The scientific program was held throughout the morning and afternoon, with the respective State Governors presiding at different sessions. In the evening there was a social hour from six-thirty, and a dinner at the George Washington Hotel at seven-thirty, at which Dr. T. Z. Cason, Governor for Florida, was the Toastmaster. Addresses were made at the dinner-meeting by Dr. Ernest E. Irons, President-Elect of the College, Chicago, Ill.; Rear Admiral Dallas G. Sutton, Envoy of the Surgeon General of the U. S. Navy, Washington, D. C.; Colonel Henry M. Thomas, Jr., Envoy of the Surgeon General of the U. S. Army, Atlanta, Ga.; Dr. Charles H. Cocke, First Vice President of the College, Asheville, N. C.; and Edward R. Loveland, Executive Secretary of the College, Philadelphia, Pa. Among other special guests at the dinner-meeting were Colonel Charles B. Callard, Director of the Medical Division, Camp Blanding, Fla., and Captain John J. O'Malley, Commanding Officer of the U. S. Naval Hospital, Naval Air Station, Jacksonville, Fla.

The annual dinner meeting of the Mississippi members of the American College of Physicians was held Tuesday, May 11, 1943, in Jackson during the annual meeting of the Mississippi State Medical Association. The dinner was well attended by mem-

bers of the College and their wives. Dr. John G. Archer, F.A.C.P., College Governor for Mississippi, Greenville, presided and the following Fellows of the College participated in the program:

Dr. G. W. F. Rembert, Jackson—"Some High Lights on the By-Laws of the American College of Physicians";
Dr. Douglas D. Baugh, Columbus—"Ways and Means of Increasing the Mississippi Membership in the American College of Physicians";
Dr. Laurance J. Clark, Vicksburg—"Some Remarks";
Dr. Wesley W. Lake, Pass Christian—"Report of a Case of Plummer Vinson's Syndrome."

Dr. Edgar Hull, F.A.C.P., College Governor for Louisiana, New Orleans, was the guest speaker. Dr. Hull spoke on "The Prospect of Public Medicine."

Dr. Homer E. Prince, F.A.C.P., Houston, spoke on "Bronchial Asthma" at a meeting of the medical students of the University of Texas Medical Branch, Galveston, May 12, 1943.

The 8th Annual Meeting of the National Gastroenterological Association was held in New York, N. Y., June 3, 1943, under the Presidency of Dr. Anthony Bassler, F.A.C.P., New York, N. Y. Among those who participated in the discussions and activities of the convention were Dr. Samuel Weiss, F.A.C.P., Dr. Max Einhorn, F.A.C.P., Dr. Thomas H. McGavack, F.A.C.P., and Dr. Henry A. Rafsky, F.A.C.P., all of New York, N. Y., Michael Lake, F.A.C.P., Lieutenant Commander, (MC), U. S. Naval Reserve, Dr. Louis L. Perkel, F.A.C.P., Jersey City, N. J., Dr. Sigurd W. Johnsen, F.A.C.P., Passaic, N. J., Henry A. Monat (Associate), Lieutenant Commander, (MC), U. S. Naval Reserve, and Dr. Hyman I. Goldstein (Associate), Camden, N. J.

Dr. Fred W. Wilkerson, F.A.C.P., Montgomery, has been elected President of the Medical Association of the State of Alabama.

Dr. Louie Limbaugh, F.A.C.P., Jacksonville, has been named one of the Vice Presidents of the Florida Medical Association.

At a regional meeting of the American College of Surgeons in Charlotte, N. C., March 22, 1943, addresses were made by Dr. Robert Wilson, Sr., F.A.C.P., Charleston, former College Governor for South Carolina, and Dr. Charles H. Cocke, F.A.C.P., Asheville, First Vice President of the College.

At the 90th Annual Meeting of the North Carolina State Medical Society held in Raleigh, May 11–13, 1943, Dr. James W. Vernon, F.A.C.P., Morganton, was installed as President and Dr. Paul F. Whitaker, F.A.C.P., Kinston, was named President-Elect.

The Press Division of the Coördinator of Inter-American Affairs is republishing in Spanish the book, "Health Officer's Manual" by Dr. Jacob C. Geiger, F.A.C.P., Director of Public Health of the City and County of San Francisco. The book has been translated by Dr. Osvaldo Cifuentes, who proposes to publish it under his direction as a publication of the Direccion General de Sanidad of the Chilean Government.

On May 22, 1943, at its commencement exercises, Duke University conferred the honorary degree of Doctor of Science on James S. Simmons, F.A.C.P., Brigadier General, (MC), U. S. Army, Director of the Preventive Medicine Division, Office of the Surgeon General.

On May 21, 1943, Dr. J. Arnold Bargen, F.A.C.P., Rochester, Minn., spoke on "The Varieties of Ulcerative Colitis" at a meeting of the Delaware Academy of Medicine at Wilmington.

The Association of Military Surgeons of the United States will hold its 51st annual convention in Philadelphia, October 21–23, 1943. This meeting will assemble physicians from all of the current war fronts where United States forces are fighting and from all the great base hospitals where rehabilitation of the wounded is in progress. Numerous forum lectures, practical demonstrations, motion pictures and teaching panels will be conducted to present the latest techniques of wartime medicine and surgery.

Ross T. McIntire, F.A.C.P., Rear Admiral, (MC), U. S. Navy, The Surgeon General, is the Honorary Chairman of this meeting, Joseph A. Biello, Captain, (MC), U. S. Navy, General Chairman; and George F. Lull, F.A.C.P., Brigadier General, (MC), U. S. Army, and Edward L. Bortz, F.A.C.P., Commander, (MC), U. S. Naval Reserve, are Vice-Chairmen.

The Executive Committee includes Captain R. H. Laning, (MC), U. S. Navy, Commanding Officer of the Philadelphia Naval Hospital, Dr. Stanley P. Reimann, F.A.C.P., Philadelphia, Dr. Gilson Colby Engel, Philadelphia, Commander J. L. Tinney, (M.C), U. S. Naval Reserve, and Dr. A. Newton Richards, Philadelphia, Vice President of the University of Pennsylvania.

Dr. Robert U. Patterson, F.A.C.P., Dean of the University of Maryland School of Medicine, Baltimore, has been appointed Consultant to the Baltimore City Health Department.

Dr. Herbert A. Burns, F.A.C.P., Minneapolis, Minn., has been placed in charge of the new Tuberculosis Control Unit in the State Division of Public Institutions.

Dr. V. P. Sydenstricker, F.A.C.P., Augusta, Ga., delivered the Eighth Harvey Society Lecture at the New York Academy of Medicine, New York, N. Y., May 20, 1943. Dr. Sydenstricker spoke on "Nutrition under Wartime Conditions."

Dr. Reginald Fitz, F.A.C.P., Boston, Mass., will speak on "The Crimson Thread" on a special program commemorating the one hundredth anniversary of the founding of Western Reserve University School of Medicine, Cleveland, Ohio, October 27, 1943.

Dr. David W. E. Baird, F.A.C.P., has been appointed Dean of the University of Oregon Medical School, Portland.

At a joint meeting of the Sixth and Seventh Councilor Districts of the Medical Society of the State of Pennsylvania, held in Williamsport, May 14, 1943, Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, spoke on "The Modern Science of Nutrition and Nutritional Deficiency" and Dr. Walter F. Donaldson, F.A.C.P., Pittsburgh, spoke on "War Participation and Organized Medicine."

Walter S. Jensen, F.A.C.P., Colonel, (MC), U. S. Army, Executive Officer in the Office of the Air Surgeon, delivered the annual Edwin J. Jarecki Memorial Lecture in Philadelphia, Pa., April 29, 1943.

Among the speakers at the annual meeting of the Iowa and Illinois Central District Medical Association held in Rock Island, Ill., May 27, 1943, were:

Dr. Italo F. Volini, F.A.C.P., Chicago, Ill.—"Clinical Observations on Heart Disease";

Dr. Charles F. McKhann, F.A.C.P., Ann Arbor, Mich.—"Progress in the Control of Communicable Disease."

Dr. Clarence E. de la Chapelle, F.A.C.P., Professor of Clinical Medicine at New York University College of Medicine, has been named Acting Assistant Dean of the University.

Dr. Titus H. Harris, F.A.C.P., Galveston, has been elected President of the Texas Association for Mental Hygiene.

Dr. Horace M. Banks, F.A.C.P., and Dr. Harold F. Dunlap, F.A.C.P., both of Indianapolis, discussed a "Case of Sarcoidosis" at the annual session of the American Society of Clinical Pathologists held in Chicago, Ill., June 3–6, 1943.

Dr. Thomas H. A. Stites, F.A.C.P., has resigned as Medical Director of the Pennsylvania State Tuberculosis Sanatorium, Cresson.

Under the Presidency of Dr. Karl J. Henrichsen, F.A.C.P., Chicago, Ill., the American Academy of Tuberculosis Physicians held its annual meeting in Chicago, June 9–10. One of the guest speakers was Dr. David Salkin, F.A.C.P., Hopemont, W. Va., who spoke on the "Treatment of Tuberculous Bronchitis."

Dr. John W. Wilce, F.A.C.P., Columbus, Ohio, has been named representative of the Ohio State Medical Association on the State Advisory Committee on Recreation and Physical Education, which is supervising the Ohio Physical Fitness Program for the Department of Education.

Dr. Chester W. Waggoner, F.A.C.P., Toledo, Ohio, has been reappointed a member of the Ohio Medical Board for the term ending March 18, 1950.

Dr. Oswald F. Hedley, F.A.C.P., U. S. Public Health Service, Bethesda, Md., addressed the Rhode Island Industrial Health Institute held in Providence, May 19, 1943. Dr. Hedley spoke on "What the Average Plant Can Do to Have an Industrial Health Program."

The annual meeting of the American College of Radiology was held in Chicago, Ill., June 6, 1943, under the Presidency of Dr. Byrl R. Kirklin, F.A.C.P., Rochester, Minn. The College sponsored a Conference of Teachers of Clinical Radiologists. During this conference Edward L. Bortz, F.A.C.P., Commander, (MC), U. S. Naval Reserve, discussed "War-time Graduate Medical Meetings."

Dr. George Baehr, F.A.C.P., Chief Medical Officer, Office of Civilian Defense, Washington, D. C., recently conferred with Mexican civilian defense officials in Mexico City on their organizational problems. While in Mexico City, Dr. Baehr spoke on "The Organization and Operation of the Emergency Medical Service" and discussed "Rescue Service."

Dr. Edward P. Eglee, F.A.C.P., New York, N. Y., has been named Chairman, and Dr. Charles H. Cocke, F.A.C.P., Asheville, N. C., Dr. George B. Gilbert, F.A.C.P., Colorado Springs, Colo., Dr. Alvis E. Greer, F.A.C.P., Houston, Tex., Dr. Foster Murray, F.A.C.P., Brooklyn, N. Y., and Dr. J. J. Singer, F.A.C.P., Los Angeles, Calif., members of the Council on Postgraduate Medical Education of the American College of Chest Physicians.

On February 10, 1943, Sharp and Dohme, Inc., of Philadelphia, received the Army-Navy "E," for excellence in production. Both the pharmaceutical and biological laboratories received the award. This was presented on behalf of the Army by Brigadier General Hugh J. Morgan, M.C., F.A.C.P., and for the Navy by Commander Edward L. Bortz, M.C., F.A.C.P. The award is well deserved, particularly for the pioneer work of this firm in developing practicable methods for the preparation of dried blood plasma on a large scale.

Dr. Edward A. Strecker, F.A.C.P., Philadelphia, Pa., President of the American Psychiatric Association, has been appointed Special Consultant to the Secretary of War for the Air Forces of the U. S. Army. Dr. Strecker is also Consultant in Psychiatry to the Surgeon General of the U. S. Navy. For some time, Dr. Strecker has been giving intensive training in psychiatry to Naval Medical Officers in Philadelphia. All of the medical and hospital facilities in this field are coöperating in the program, three months in length. In World War I he served as Major in the Army Medical Corps, as Division Neuropsychiatrist for the 28th Division in France.

Dr. Strecker is Professor and Head of the Department of Psychiatry of the Graduate School of Medicine and in the Medical School of the University of Pennsylvania. Since 1917, he has been Medical Director of the Pennsylvania Hospital

Department of Nervous and Mental Diseases. He is Chief of Service at the Institute for Mental Hygiene of the Pennsylvania Hospital and Consultant to Bryn Mawr College and the U. S. Veterans Bureau.

The Omaha Mid-West Clinical Society will hold its eleventh annual assembly October 25–29 at the Hotel Paxton, Omaha, Nebraska.

Among the speakers who have accepted places on the program are Dr. James E. Paullin, F.A.C.P., Atlanta, Ga.; Dr. Tom D. Spies, F.A.C.P., Birmingham, Ala.; Dr. Harold G. Wolff, F.A.C.P., New York, N. Y.; Dr. Eben J. Carey, Milwaukee, Wis.; Dr. Sanford R. Gifford, Chicago, Ill.; Dr. L. Emmett Holt, Jr., Baltimore, Md.; Dr. Frank R. Ober, Boston, Mass.

Friday, October 29, will be devoted to a symposium on "War Medicine and Surgery." The participants will be physicians of the United States Naval Medical Corps. There will also be other periods in the program devoted to problems confronting the Medical Corps of the United States Army. Scientific and technical exhibits, along with a moving picture program, will complete a five-day meeting.

OBITUARIES

DR. CLAUDE W. ASHLEY

Dr. Claude W. Ashley, F.A.C.P., Bloomsburg, Pa., born February 2, 1905, died suddenly on May 22, 1943.

Dr. Ashley was born in St. Louis, Missouri, and graduated from the William Jewell College in Missouri, in 1928. He received his degree of Doctor of Medicine from Jefferson Medical College of Philadelphia in 1932.

For two years, Dr. Ashley served as Resident in Pediatrics at the Children's Hospital in Cincinnati, and from 1934 to 1935 he was Resident in Internal Medicine at the Geisinger Memorial Hospital in Danville, Pennsylvania.

Dr. Ashley has been outstanding in the medical activities of his community and has been a true servant of his profession throughout the short time of his practice. At the time of his death, he was Chief of the Medical Service, Chief Pediatrician and Vice President of the Staff of the Bloomsburg Hospital. He was a Diplomate of the National Board of Medical Examiners and also a Diplomate of the American Board of Pediatrics. Dr. Ashley also served as former Secretary and President of the Columbia County Medical Association.

Medical society memberships included the Pennsylvania State Medical Society, Fellowship in the American Medical Association and Fellowship in The American College of Physicians.

Dr. Ashley's untimely death has come as a great shock to his many friends and colleagues and it is with sincere regret that we acknowledge his passing.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. GEORGE B. LAKE

Dr. George B. Lake (Associate) was born in Topeka, Kansas, November 26, 1880, and died in the Lake Forest Hospital, Lake Forest, Illinois, March 2, 1943.

He received his formal education at Wheaton College, the University of Michigan, and graduated from Rush Medical College in 1902. The next two years he spent as Assistant Surgeon of the Mexican Central Railway Hospital. It was probably during this time that he acquired command of the Spanish language. From 1908 to 1910 he was special lecturer in Rural Hygiene and Sanitation at Purdue University.

In 1910 he entered the Medical Corps of the U. S. Army. He graduated from the Army Medical School in 1911 and took part in the Philippine campaign in 1913. He was on General Pershing's staff during the invasion of Mexico and was selected as one of the force of specially picked men who

left the main body of the army to make a grilling and hazardous dash after the bandit Villa. He served in the Medical Corps until 1924 and resigned with the rank of Major. Later he became a Colonel in the Medical Reserve Corps of the Army.

In 1924 he assumed editorship of the journal which later became Clinical Medicine and Surgery, and in 1934 he became editor and publisher of that journal.

He was a poet of considerable ability and published a number of volumes of poems. At one time he was President of the London Poetry Society.

He was interested in mysticism, philosophy, psychiatry and metaphysics. He was deeply religious and was a priest of the Liberal Catholic Church and often conducted services in the Church of St. Francis in Chicago.

He was a member of the Chicago Medical Society; the Illinois State Medical Society; the Mississippi Valley Medical Society; the Association for the Study of Internal Secretions; the American Association of the History of Medicine; the Association of Military Surgeons of the United States; the Mississippi Valley Medical Editors' Association, of which he was President during 1941; and a Fellow of the American Medical Association. Dr. Lake was a member of the American Congress on Internal Medicine and became an Associate of the American College of Physicians when the College and the Congress merged.

His philosophy of life gave him tranquillity and joy beyond the experience of most men.

James H. Hutton, M.D., F.A.C.P.,
Chicago, Ill.

DR. ARTHUR E. DAVIS

Dr. Arthur E. Davis, Scranton, Pennsylvania, died at his home on May 2, 1943, after an illness of one week.

Dr. Davis was born at Avoca, Pennsylvania, on March 25, 1887. He attended Hillman Academy and graduated in medicine from the Medico-Chirurgical College of Philadelphia in 1911.

He was, for many years, Visiting Chief at the West Side and Scranton State Hospitals, and Cardiologist at the Mercy Hospital. Dr. Davis was former President of the Lackawanna County Medical Society; he held membership in the Pennsylvania State Medical Society and the American Medical Association. Since 1928, he has been a Fellow of the American College of Physicians.

The sudden death of Dr. Davis has come as a great shock to his many friends and colleagues throughout the entire State. He has been held in high esteem as an internist of renown and it is with a deep sense of loss that his passing is acknowledged.

Edward L. Bortz, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. ALBERT HAMMOND HOGE

Dr. Albert Hammond Hoge was born at Hoge's Store, Giles County, Virginia, August 17, 1885, the son of Samuel S. and Mary Price Hoge. After graduating from Mayfield High School he entered Massey College, Richmond, Va., in 1903. The next year he matriculated at the University College of Medicine, Richmond, where he graduated in 1908. After graduation he served a year's internship at St. Luke's Hospital, Richmond. In the fall of 1909 he located in Bluefield, W. Va., where he became associated with Dr. Charles M. Scott in the management of St. Luke's Hospital, where he remained continuously, being Medical Director at the time of his death.

Dr. Hoge early in his professional career became an outstanding physician and a leader in organized medicine. He served as president of the Mercer County Medical Society and in 1932 was president of the West Virginia State Medical Association. He was a Fellow of the American Medical Association, and in 1924 he was elected to Fellowship in the American College of Physicians. In 1939 he became a member of its Board of Governors. In 1930 Governor Conley appointed Dr. Hoge to membership on the West Virginia Public Health Council which combines the functions of both a state board of health and a state board of medical examiners. He was a member of this body for twelve years, served as president from 1933 to 1937. Dr. Hoge was a Diplomate of the American Board of Internal Medicine.

A convincing speaker and a lucid writer, he was the author of numerous articles on medical subjects. Strangely enough, his last article was the obituary of Dr. Charles W. Waddell, published in the May issue of the ANNALS, which was received by the Philadelphia office after Dr. Hoge's death. Shortly after graduation he was elected to membership in the Medical Society of Virginia, which membership he very appropriately maintained until his death inasmuch as he resided very close to the state line and drew a large clientele from both his native and adopted states.

Not only was Dr. Hoge an outstanding physician but he was an outstanding citizen. He was a Mason and a Shriner, a past president of the Bluefield Rotary Club, and an official of the Community Savings and Loan Association. In company with his brothers, he operated his large ancestral estate in Giles County as a stock and apple farm. He served in the Army Medical Corps in World War I. He was in faith a Presbyterian and in politics a Democrat. His friends were legion throughout both the Virginias. He was an ardent devotee of both rod and gun and one of the best shots in the entire South.

Shortly before midnight on April 7, Dr. Hoge suffered a very severe coronary occlusion and died in an ambulance en route to the hospital. A fortnight before he had been slightly indisposed but he felt he had recovered and had worked regularly the last few days preceding his sudden fatal attack.

West Virginia has lost an outstanding citizen and the medical profession a stalwart member.

WALTER E. VEST, M.D., F.A.C.P.,
Governor for West Virginia

DR. ANDREW SLOAN

Dr. Andrew Sloan (Fellow, 1922) was born in Utica, N. Y., January 5, 1880, with a professional background which assured him scientific acumen and high ethical principles, for his father, Dr. Hugh Sloan, had been an outstanding physician of a generation now past and his mother, Elizabeth Wetzel Sloan, was the daughter of a Lutheran clergyman whose memory is still green among the older citizens of the community.

Andrew Sloan, upon being graduated by the Utica Free Academy, studied medicine at the College of Physicians and Surgeons of Columbia University and was graduated there in 1902. For the past forty-one years he has been a practicing physician as an internist in Utica, particularly interested in hospital administration.

On the retirement of Dr. Willis Ford as Medical Director of St. Luke's Hospital in 1921, Dr. Sloan was his logical successor and immediately assumed the position which he held for more than a decade. His influence was manifest in the hospital and to him is due to no small extent the high medical and ethical standing of that institution. When the Utica Visiting Nurses and Child Health Association was formed Dr. Sloan became chairman of the Medical Advisory Board. The growth of this potent civic institution during the past fifteen years is a measure of his efficiency and public service spirit.

In 1921 Dr. Sloan became vice-president of the Medical Society of the County of Oneida and the following year its president. The Medical Society of the State of New York recognized his services in its House of Delegates over many years by electing him First Vice-President and sending him as a delegate to the American Medical Association.

Dr. Sloan was also a past president of the Utica Medical Club, a member of the Fort Schuyler and Yahnundasis Clubs, and of the Masonic Fraternity.

Dr. Sloan will be long remembered as the founder and, for its first ten years, the president of the Utica Academy of Medicine. Here his enthusiasm, his professional zeal, and his insistence that the Academy should maintain the highest standards and become a post-graduate school for his fellow physicians of the Mohawk Valley, launched the Academy on a career of great usefulness to its members and influence throughout New York State.

He leaves a wife, Margaret Diefenbach Sloan, and three brothers, Hugh Sloan, Samuel Sloan and Dr. Robert Sloan, a past president of the Oneida County Medical Society.

WILLIAM A. GROAT, M.D., F.A.C.P.,
Syracuse, N. Y.

DR. JOHN HYREN PECK

Dr. John Hyren Peck, F.A.C.P., was born at Lost Nation, Iowa, August 3, 1879; he died at his home at Oakdale, Iowa, October 18, 1942, of coronary thrombosis.

Dr. Peck attended the public schools of Olin, Iowa, and the State University of Iowa, from which he received the degree of M.D. in 1909. Following an internship at the State University of Iowa, he entered the practice of medicine in Des Moines. He developed an early interest in diseases of the chest, and in 1912 served as resident physician in the State Sanatorium at Oakdale, after which he resumed practice in Des Moines. In 1936, he became superintendent of the State Sanatorium.

Dr. Peck served as president of the Polk County Medical Society, the Iowa State Medical Society, the National Tuberculosis Association, and the American College of Chest Physicians; he was president of the Iowa Tuberculosis Association from 1918 to 1934. He became a Fellow of the American College of Physicians in 1930. During World War I, he served as a Major in the U. S. Army Medical Corps, and was chief of the tuberculosis service at the base hospital at Camp Dodge. He was certified by the American Board of Internal Medicine.

The most unique, and possibly the most fruitful feature of Dr. Peck's professional career was his educational activity in the field of tuberculosis. Almost single-handedly, he made the State of Iowa, medical and lay, tuberculosis conscious. For twenty years, in addition to caring for a busy practice, he conducted diagnostic clinics and gave addresses on tuberculosis in every county in the State. He knew nearly every physician in the State by his first name, and was regarded affectionately by all of them. He well deserved the high honors which came to him.

B. F. Wolverton, M.D., F.A.C.P.,
Governor for Iowa

DR. JOHN TAYLOR WATKINS

Dr. John Taylor Watkins, F.A.C.P., Detroit, Mich., died of cerebral hemorrhage, May 8, 1943.

Born in Whitmore Lake, Michigan, in 1883; he graduated from the University of Michigan Medical School in 1906. After one year of general practice in the Upper Peninsula of Michigan, he moved to Detroit, where he later confined his work to Internal Medicine. Until ill health necessitated his retirement six and one half years ago, Dr. Watkins enjoyed a large and select practice in his chosen field. An able clinician, he had those personal characteristics that inspired confidence and endeared him to his patients. Meticulous in dress, scholarly in diction, gentle and dignified in manner, he radiated that professional atmosphere that all admire but few possess.

During his active career he was honored with the following appointments and memberships: Professor of Clinical Medicine at the Detroit College of Medicine and Surgery, now Wayne University College of Medicine; Physician-in-Chief and Vice Chief of Staff to the Grace Hospital; Chief of Staff at the Woman's Hospital; Consulting Physician to the Highland Park General Hospital; member of the Wayne County Medical Society, Michigan State Medical Society, American Medical Association, the American Therapeutic Society and had been a Fellow of the American College of Physicians since 1920.

Besides his immediate family and relatives he leaves a host of friends, both lay and professional. It is with deep regret that we mark his passing.

P. L. LEDWIDGE, M.D., F.A.C.P.,
Acting Governor for Michigan